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

Part 1	**General information**
Inspected site	
Name and Address of inspected site	Clinical and Bioanalytical site Norwich Clinical Services Pvt. Ltd Ground and First floor, 147/F, 8th Main, 3rd Block Koramangala, Bangalore - 560 034, Karnataka, INDIA
Corporate address of Organization	Norwich Clinical Services Pvt. Ltd., 147/F, 8th Main, 3rd Block, Koramangala, Bangalore - 560 034, Karnataka, INDIA
GPS coordinates	Latitude: 12.9286 Longitude: 77.6286
Inspection details	
Dates of inspection	18 – 22 June 2018
Type of inspection	Routine
Introduction	
Brief description of activities performed at the site	Norwich Clinical Services (NCS), a CRO, conducts Phase I to IV clinical research and provides Pharmacovigilance and training services. The facility has the capacity to perform the clinical phase, bioanalytical and statistical analyses of bioequivalence / bioavailability in healthy subjects and/or patients. The CRO contracted out the clinical pathology analyses.
General information about the company and site	Norwich Clinical Services initially started operations in 2010 with pharmacovigilance services. Subsequently, the company expanded to include bioanalytical and clinical services, conducting studies for submission to the FDA, WHO, ANVISA and EU. The Pharmacovigilance services were housed in a separate building and did not form part of the inspection. The clinical and bioanalytical services were housed in the same building and the statistical services were in a separate building next door.

History	The company was inspected once by the MOH of Turkey and the EMA, 4 times by the US FDA, and several times by the CDSCO, India. The CRO was previously inspected by the WHO in January 2014. The list of inspections was provided.
Brief report of inspection activities undertaken – scope and limitations	
Areas inspected	The Inspection team covered study-related activities of the four studies included in the scope of the inspection. The company's history, clinical study performance, informed consent process, ethics committee approvals and correspondence, test article accountability, dispensing and storage, processing and handling of biological (plasma) samples collected during the study, equipment calibration, employee training, computer controls, were reviewed and a tour of the facility taken. Regarding the Analytical operations, the team covered confirmation of good practices, qualifications of personnel and procedures used during the method validations and analytical testing. The clinical study data, analytical method validation, and analytical study data were reviewed, and the source data compared to the study reports.
Restrictions	N/A
Out of Scope	N/A
WHO product names covered by the inspection, study title, sponsor	**Study no: NCS-563-17-BA** An open label, randomized, balanced, single dose, two treatment, two period, two sequence, two-way crossover oral bioequivalence study comparing Fixed dose combination of Rifampin 150 mg, Isoniazid 75 mg and Ethambutol Hydrochloride 275 mg Tablets (1 x 04 Tablets) of Lupin Limited, India with separate formulations of Rifamate® (Rifampin 300 mg and Isoniazid 150 mg) capsules (1 x 02 Capsules) of Sanofi Aventis, USA and Myambutol® (Ethambutol Hydrochloride) tablets 400 mg (1 x 03 Tablets) of RiemserArzneimittel, Germany, in healthy adult human male subjects, under fasting conditions.

	Study no: NCS-561-17-BA A Randomized, Open Label, Balanced, Single Dose, Two Treatment, Two Period, Two Sequence, Two Way Crossover Oral Bioequivalence Study Comparing of Fixed Dose Combination of Rifampin And Isoniazid Tablets 150 mg/150 mg (2 x 150 mg/150 mg Tablets) Manufactured By Lupin Limited, India With of Rimactan (Rifampicin) Capsules 300 mg (01 Capsule) Manufactured By Sandoz Farmaceutica S.A., Spain & Isozid (Isoniazid) Tablets 100 mg (3 x 100 mg Tablets) Manufactured By Fatol Arzneimittel Gmbh, AG An Derwiek 7, 17493 Grcifswald-Insel, Riems Germany In Healthy Adult Human Male Subjects, Under Fasting Conditions. **Study no.: NCS-570-17-BA** An Open Label, Balanced, Randomized, Single Dose, Two-Treatment, Two-Sequence, Two-Period Crossover Bioequivalence Study Comparing **Akurit** 4 (Rifampin 150 mg, Isoniazid 75 mg, Pyrazinamide 400 mg and Ethambutol Hydrochloride 275 mg) Tablets (1 x 04 Tablets) of Lupin Limited, India with Reference Products as separate formulations of Rifamate® (Rifampin 300 mg and Isoniazid 150 mg) Capsules (1 x 02 Capsules) of Sanofi Aventis, USA, Pyrafat® (Pyrazinamide 500 mg) Tablets (1 x 03 Tablets) of Riemser Arzneimittel AG, Germany, Myambutol® (Ethambutol Hydrochloride 400 mg) Tablets (1 x 03 Tablets) of Riemser Arzneimittel, Germany, in Healthy, Adult, Human Male Subjects Under Fasting Conditions. **Study no: NCS-585-17-CS** A randomized, open label, balanced, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study comparing **fixed dose** combination of **Rifampicin 75 mg and Isoniazid 50** mg **Dispersible** Tablets (2 Tablets) of **Lupin** Limited, India with Rifampicine Capsules 150 mg (1 Capsule) of **Sandoz** BV Veluwezoom 22, 1327 AH Almere The **Netherlands** and **Isozid** (Isoniazid) Tablets 100 mg (1 Tablet) of **RlEMSER** Pharma GmbH, Ander Wiek 7 17493 Greifswald-Insel Riems in healthy, adult, human male subjects under **fasting** conditions.

Abbreviations	Meaning
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
eCRF	(electronic) case report form
CRO	contract research organization
CoA	certificate of analysis
CS	calibration standard
CSR	clinical study report
CSV	computerized system validation
ECG	electrocardiogram
F/T	Freeze thaw study
GCP	good clinical practice
GLP	good laboratory practice
HPLC	high-performance liquid chromatograph
HQC	high concentration quality control standard
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	(independent) ethics committee
IMP	investigational medicinal product
IS	internal standard
ISR	incurred sample reanalysis
ISV	internal standard response variation
JD	job description
LC-MS/MS	liquid chromatography–mass spectrometry
LIMS	laboratory information management system
LLOQ	lowest limit of quantification
LOD	limit of detection
LTS	long term stability
MVR	monitoring visit report
OQ	operational qualification
P&A	precision and accuracy
PIS	patient information sheet
PQ	performance qualification

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

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

1. Organization and management

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

The organization was started in 2010 as pharmacovigilance service provider, and later expanded their business to bioanalytical activities in 2011 and clinical activities in 2012 at a hospital location which was covered by a previous WHO inspection. The organization was managed by Dr. Saral Thangam as CEO.

The company consisted of two facilities (see Annexes I and II) as mentioned in the CROMF.

Annex I housed the medical writing, PK, bio-statistics, Regulatory affairs, clinical trial, administration, quality assurance and training units. Annex II housed the Pharmacovigilance (PhV) unit.

Norwich Clinical Services Pvt. Ltd. had received approval for BA and Clinical activities from the local authority (Directorate General of Health Services) on 18 Sept 2017. A certification for the clinical facility was issued on 27 Jul 2017 valid for a period of three years from the date of issue.

Organograms were dated and authorized 14 May 2018, illustrating the general units consisting of the Pharmacovigilance unit, BA-BE and GLP Unit, Clinical unit, QA and Validation Unit, Regulatory Affairs, PK-Reporting and Biostatistics, Business Development, Project Management, Medical Writing, IT, Training Unit, Finance and Commerce and Administration Units with names of staff. Names of contracted staff were separately added as annexes. The Validation Unit was staffed by engineers responsible for calibration and maintenance of instruments, as well as validation of software.

About 137 people were employed at the CRO at the time of inspection.

The normal working hours were from 09:00 to 17:00/17:30. When necessary a first shift 07:00 to 15:30 and a second shift from 14:00 to 22:30 would be added.

Previous inspection findings

Findings from the previous inspection were reviewed and verified. The implemented processes for line clearance and dispensing could not be verified as there was no trial taking place at the time of inspection. However, the documentation outlining the process was available.

2. Computer systems

The organization provided a list of software that was used within the organization. The IT department was responsible for the maintenance of computers, back up of data and installation of programmes and software systems. All computer programmes were date stamped. Time and date were controlled by a central computer that was linked to GPS time. The ability to change the date and time on computers was controlled by the IT department. A documented process was in place that required approval from multiple departments before time and date stamps could be altered. Any alteration was recorded in the Server Time Synchronization log book. The audit trail for date and time checking for the last 12 months was reviewed. Audits were performed monthly and recorded in the log book. On two occasions, the time was altered (out by 1 minute and 10 seconds and 1 minute and 19 seconds) and the process was followed according to the respective SOP. The Email chain between the different departments informing them of the time difference and the requirement to alter the time was available.

Validation

The company had a mature and well-established process for the validation and revalidation of equipment and software systems. All items were revalidated on a 3-yearly cycle with a revalidation plan available. All plans, protocols and reports were prepared, reviewed and approved by a number of people from different departments. Roles and responsibilities were clearly established within the Validation Master Plan. Objectives within this document were clearly defined. An initial Risk Assessment process was performed, followed by design qualification, validation plan and protocol and at completion a validation report was available. All validation plans, and reports required the approval from a number of departments before being implemented. A list was available for all software systems and equipment validation plans and time when due, for review.

When a new version of software system was to be implemented a change control request was raised.

The Software access control list was available for all software systems used within the facility. (List dated 5 June 2018 reviewed)

Volunteer Database Software (VDS)

VDS was used for the collection of volunteer information. The software had been validated and the validation report was reviewed.

The following documents were included in the validation of the Volunteer Database software:

- Performing Validation Activity
- Design Qualification for Volunteer Database software Validation Protocol for Volunteer Database software, including the validation of the audit trail (1 Aug 2016).
- Validation report for Volunteer Database software

The Volunteer patient data base was validated on 6 Aug 2016 with the next due 5 Aug 2019.

Stock Dilution Manager

The Stock Dilution Manager Software system was demonstrated. The programme including the audit trail had been validated.

The following documentation and reports were reviewed:

- User requirements specifications for Stock Dilution Manager Software (STDMS)
- Revalidation Report for Stock Dilution Manager Software
- Risk Assessment for Stock Dilution Manager Software

Scientific Data Management Software (SDMS)

The Scientific Data Management Software and Scientific Data Reporter Management Software system were used within the organization. All validation records and reports were available:

- Revalidation plan for Scientific Data Management Software
- Revalidation Protocol for Scientific Data Management Software. The revalidation of the audit trail was included in this protocol.
- Revalidation Report for Scientific Data Management Software.

The URS for SDMS software was reviewed.

The following parameters are 100 % QC-ed in SDMS software:
Schedules, result table, calibration curves, chromatogram, audit trail and batch acceptance.

Analyst Software

Bioanalysis of subject samples was performed using validated software system. The organization had used a total of three mass spectrometers in the studies in the scope of the inspection.

The following documents were included and reviewed in the validation of the Analyst software

- Validation Plan for Analyst 1.6.3 software
- User requirement Specifications for analyst 1.6.3
- Test Plan for analyst 1.6.3
- Change Control form
- Installation Qualification for Analyst 1.6.3 software
- Operational Qualification for analyst 1.6.3 software
- Performance Qualification for Analyst 1.6.3 software
- Analyst Software 1.6.2
- Analyst Software 1.6.3
- Analyst 1.6.3 software – Risk Assessment document

Overall the company had a strong and robust validation and revalidation process.

Access control
All areas were controlled with access control cards except for the ICU area. A process was in place for installing access control to this room with permission being provided to the doctors and nurses on site. IT department were responsible for granting permission to secure areas within the facility. Staff within the organization were able to demonstrate effectiveness of the implemented restricted access.

Procedures for back-up
Backups were written in Tape Media and were performed daily, weekly and monthly.

The SOP for Data backup and archival policy was reviewed.

The company had a procedure to check the correctness of the backed-up data within regular time intervals. The documentation for the last check/verification in March 2018 was done for randomly selected tapes from different projects. The SOP for Quality assurance – General activities was reviewed. At least once in six months QA personnel randomly selected few files from the archived data on the tape media which contained the backup data from the chromatography software system, and other databases to confirm that the files could be viewed or opened directly, hence only the readability would be verified.

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

3. Quality management

The QA was an independent unit reporting directly to the CEO. In addition, every unit had an internal QC system in place. The QA unit was divided into three groups: BA-QA, CL-QA and CT-QA. The unit consisted of 10 members, who were also in charge of QMS.

A software program used for SOP management was enabled to generate notification to the QA-team of the expiry time of the SOPs. The software was customized by the IT-unit. The SOPs were all uploaded into the system, with read-only access to the designated personnel.

QA was responsible to conduct internal audits, facility audits, vendor audits, project specific audits in the clinical units, clinical trials unit, BA lab and PhV, including random checks of processes across the units.

The internal vendor audit schedule for 2018 was provided, as well as the signed and dated service agreements and renewals with an X-ray centre and pathological laboratory.

The CRO Master File (CROMF) was reviewed and verified to be compliant.

The list of SOPs reviewed and verified was provided in the CROMF Annex 11. The following SOPs were reviewed:

- SOP for Bioanalytical Method Development
- SOP for Bioanalytical method validation
- SOP for chromatogram integration and acceptance criteria.
- SOP for Vendor audits
- SOP for Operation, handling and calibration of automatic pipettes
- SOP for procedure for archiving and ensuring the safety and security of the Archives
- SOP for Data Backup & Archival Policy
- SOP for maintenance activities
- SOP for Issue and Archiving of logbooks

Another software program connected to the SOP management system for training purposes, was available. Training on a SOP was notified to designated personnel from the day the SOP was ready with a deadline of three days. The QA-team received an automated list of those who did not perform the training within the deadline in the software system. Those employees were not allowed to carry out the respective activity before they had received the training.

An audit plan for vendor audit schedule 2018, prepared by the QA-unit in the beginning of the year was provided. 15 vendors were listed on the schedule, including the X-ray facility and the Laboratory for pathology.

The agreement with the X-ray facility dated 21 Feb 2018 was provided with pertaining accreditation of the facility.

The schedule for revised internal audit 2018 was also provided in April 2018.

QA was responsible for issuance of the templates and forms required for record of study data, when requested by the respective department. A form was available to record the reconciliation of project specific forms. Unused forms were identified by striking them through and were kept with the rest of the used forms.

SOP for Internal Audits: Conduct, Follow-up was revised to include the information regarding preparation of the internal audit schedule.

4. Archive facilities

The archive facilities had been moved from the 1st floor to the Ground floor. According to the documented process a change control had been submitted and the temperature and humidity mapping had been performed on the relocated facility.

The facility was orderly and clean with restricted access. The staff member responsible for the area was knowledgeable in his role and responsibilities. The Retention period of all documents was 20 years. There was no destruction procedure in place as it had not been required. However, a draft procedure was presented at the end of inspection. The area was fumigated monthly and rodent traps were checked every 15 days by an external company.

Appropriate fire control equipment was available in the facility with a fire proof door. There were no windows within the room as it was an internal room.

The Archival record log book and the procedure for archiving and ensuring the safety and security of the archives were reviewed. Temperature and humidity parameters assigned to this facility were in a temperature range from 19 to 26 °C and Humidity between 30-60 %.

5. Premises

During the inspection, a tour of the facility was conducted. This facility was clean, organised, tidy, looked professional and was very well maintained.

The facility plan layouts for all facilities were provided in the CROMF.

There were two wards within the facility, both equipped with alarms. The toilet facilities were clean with alarms within the toilets in working order. Meals were provided for all volunteers during the trial. A central eating area was available between the two wards. A games and television area was available for volunteers to use during trial periods.

The restricted areas were accessed by only authorized personnel using individual access cards. Synchronized clocks are located throughout the facility to enable documenting the exact time study activities occur.

Screening area

The screening area was clean and temperature controlled with a television provided for volunteers. The process of screening volunteers was orderly. Private rooms were available for the collection of blood samples, ECG monitoring and urine collection.

At the time of inspection, the ladies' toilets in the screening area were inspected.

CPU

The Clinical unit was located on the ground floor. The CPU division was divided into two wings located on the first floor. A form for maintenance activities was completed every day.

ICU

The ICU was located between the two wards. The facility was locked and the security guard would provide the key when required. This was discussed and access control using a swipe card was to be implemented.

The medication available for emergencies was regularly verified for the expiry date by reviewing the usage and maintenance log of ICU medications, which was found to be compliant.

An anaphylactic kit was available and checked prior to each study. Documentation reviewed was Maintenance of ICU and Ambulance Medications.

The use of the ambulance during trial periods was reviewed.

Sample processing room

The room was adjacent to the collection room. The centrifuge within the room was well maintained. A marble bench allowed easy cleaning and decontamination in case of spill. A haemolysis chart was available on the wall beside the centrifuge for the recording of samples.

Monitoring of temperature and humidity

The facility was temperature controlled. All refrigerators and freezers were temperature monitored with log books available for the recording of temperature. Of the log books reviewed there were no deviations recorded.

Safety measures

The First aid kit was available in the entrance to the analytical laboratory and material safety data sheets were available within the laboratory.

Disposal of waste and other environment-friendly measures:
The disposal of waste was performed by an external company.

Bioanalytical lab
The Bioanalytical laboratory consisted of a number of rooms. There was a preparation area where buffers were made and samples and QCs prepared. Material Safety Data sheets were available. All prepared buffers were adequately labelled. A safety shower and eye wash station were available.

The premises were equipped with 2 UPS units supplying the clinical units, computers and laboratory devices and the emergency lamps.

A generator with 250 KVA capacity was kept in a secured room, working with diesel as fuel, equipped with an indicator for usage of the fuel. Maintenance was performed by checking the radiator water and oil water on a daily basis.

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

6. Personnel

A complete list of employees and their designation kept as an Excel sheet in the system was provided by HR. The facility was also using staff on one year contracts.

CVs and JDs of employee's delegated tasks according to the delegation list pertaining to the study NCS-585-17-CS were randomly selected for review and verification. The delegation list was properly completed.

Training was conducted as induction training to the newly recruited employees including both general training and job specific training. In addition, GxP training, any other relevant and refresher training/topics would take place at least once a year.

The training SOP and training documentation of a selection of employees were reviewed.

The process for the termination of the employee who had recently left the company was reviewed. The employee had submitted his resignation. The termination process consisted of removal of his access to emails, returning his access card, and other relevant practicalities.

The Observation made in relation to the personnel was addressed in the CAPA plan provided by the CRO.

Clinical section

7. Clinical phase

A dosing day was not scheduled during the inspection, and dosage administration was therefore not observed. However, the facility was well-maintained.

A Master services agreement with the sponsor Lupin was provided, signed on 2 Jun 2015. The CRO was required to keep the biological samples for a period of 3 month after the results were submitted to the sponsor.

Agreement with hospital in case of emergency
NCS had contracts with two local hospitals in place. Prior to commencing a study, NCS contacted the local hospital and informed them of the type of study, molecule and dosage that would be administered including the duration of the study. This was via email and all communications were filed within the TMF.

Mock drills were conducted once every 6 months. The drill included contacting the hospital informing them of the mock study, dosage, molecule being administered and time to transport patient to that hospital. Only one hospital was notified per study.

8. Clinical laboratory

Clinical/Pathology laboratory
The biological samples were transported along with the test request form under controlled temperature conditions for analysis to the pathology laboratory, which was accredited by NABL, and CAP.

An Accreditation certificate from the College of American Pathologists was available. Re-inspection was planned for 2 May 2020.

Laboratory normal ranges were included in the respective SOP and submitted to the Ethics Committee for approval.

9. Ethics

ACE Independent Ethics Committee approved the study protocol on 22 Jan 2018 and a correction of the food menu on 02 March 2018.

The list of 11 members was reviewed and included a clinician (chair), secretary, basic medical scientist, theologian, legal and lay person.

The General documentation was appropriately submitted for approval by the Ethics Committee.

A plan for advertisement to invite the volunteers for the studies was provided, approved by EC on 7 Nov 2017. Back translation of Kannada to English was also provided which was verified in an approval letter by ACE IEC on 2 Mar 2018.

An insurance policy was held with "National Insurance Company Ltd".

10. Monitoring

Monitoring reports were reviewed, without any remarks.

11. Investigators

CVS and JDs of investigators attending the study NCS-585-17 were reviewed, together with their GCP certifications.

12. Receiving, storage and handling of investigational drug products

Pharmacy

The Pharmacy was well controlled and compliant with access records for each visit, the logbook kept in a neat built in cupboard at the entrance. The pharmacy and medication archive room were temperature and humidity compliant.

Dispensing by the pharmacist was witnessed by the Study investigator who countersigned the UV light and laminar airflow logbooks. One treatment was dispensed at a time under laminar air flow.

The medicine archive was securely locked area accessible to only the authorized pharmacists, opposite the pharmacy, and study medicines were readily identifiable and retrievable.

The refrigeration facilities for storage of relevant medicines in both the pharmacy and medicine archive were adequate and had compliant and functional temperature and alarm controls.

The refrigerator alarm in the medicine archive was tested to verify proper function of the alarm and notification procedure. The Internal security GLP engineers notified the pharmacist that the alarm had been activated.

Relevant Pharmacy records e.g. request for the required quantity of study treatments from sponsor, the certificates of analysis and shipment documents, were kept in the Study Trial Master file. This was subsequently confirmed during the review of the Study Trial master files. The randomisation list was received from the Biostatistician, the labels were prepared in the pharmacy as a hard copy and checked by QC. Perforation of the labels using a perforator was demonstrated.

Yellow monochromatic light was available and was used while dispensing the relevant study medication, even though not required by the labelling of the study products.

The remaining/archived study medicine quantities were verified as recorded.

13. Case report forms

CRFs provided for study number NCS-585-17-CS were reviewed for randomly selected subjects. Clinical reference parameters were found to be within specified limits of references as stated in the protocol. When post study sample results were identified as being outside of the acceptable range, volunteers were retested. Post study testing was generally related to high cholesterol or glucose levels.

Acceptable range for laboratory parameters Document number CL-052-07, effective date 7 Feb 2018 was reviewed.

14. Volunteers, recruitment methods

Recruitment

The clinical site had recently relocated to the Ground and 1st floor of the main building in the location mentioned in this report. The clinical site was previously located in a hospital where they had number of volunteers. Hence, the site was already known and recruitment of new volunteers took place by word of mouth.

Registration

A Volunteer database system was used to register the volunteers.

The registration activities were observed by the inspectors. The volunteer was biometrically registered using fingerprints of all 10 fingers.

The OVIS database was used to avoid the cross participation of the volunteers in different CROs registered in the database, by identification of their fingerprints.

The database had an option called "Report" to run the subject screening log based on the name of the project.

The SOP for Check list for audit of computer systems/software was available and indicated significant oversight of the system. An upgrade of the volunteer database system was already processed.

The Computer system audit trail of volunteer database software dated 27 Jul 2017, was reviewed.

The Alcohol Breath Analyzer device was demonstrated. The process would be done prior to the check-in process for each volunteer. A new equipment with an indicator to ensure that sufficient amount of lung-air was blown into the device before the actual measurement started, was provided on Day 3.

The informed consent process was verified.

A general screening ICF would be signed prior to the screening of volunteers. All general screening ICFs pertaining to study NCS-585-17 were reviewed. In the second phase, the volunteer would meet with the physician to discuss the advantages and disadvantages of the study. The general consent covered the whole screening activities. The Physical examination was performed after the signing of the ICF.

Subsequently, prior to the check in, another study specific ICF would be signed. All 36 ICFs were reviewed and compared with the visitor logbook.

ECG

ECG was performed using GE Healthcare machine MAC 2000. The instrument did not have a memory function. The process was done by the educated nurse, entering the patient ID, age and gender. Only the GLP engineer had the access to change the time to synchronize the clock with the GPS-coordinated clocks used in the facility. The ECG screening of a subject was observed and regarded adequate.

The ECG results for the studies NCS-593-18-CS, NCS-427-15-CS and NCS-585-17 were studied.

15. Food and fluids

The preparation of the food was outsourced to a catering facility through an agreement made on 3 Aug 2017 for one year.

The audit report was provided. The audit took place on 27 Feb 2018 and an audit was planned/conducted once a year in the last 10 years.

The time of food provided and drinks was recorded in the CRFs, with notes if a meal had not been eaten.

16. Safety, adverse events, adverse event reporting

All adverse events related to study NCS-585-17 were recorded. Of the 13 records reviewed there were two reported adverse events, both were documented.

Bioanalytical section

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

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

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

Audit trails for runs MV-077-01 Rifampin + metabolite, MV-077-02-Rifampin+metabolite MS01 & MS02 were reviewed and verified.

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

Study no.:	**NCS-563-17-BA**
Method development Data was adequately recorded and readily retrieved.	
On 2 Dec 2016, Specificity and selectivity in method development was demonstrated for both Rifampicin and Desacetyl Rifampicin. 6 plasma samples in addition to Lipemic and Haemolytic samples were provided and verified. Similarly, no interference was demonstrated for INH, by providing 6 plasma samples in addition to Lipemic and Haemolytic samples. Documentation dated 22 Dec 2016 was reviewed and verified. Literature references were separately filed and not referred to in the Summary but were readily available on request. During a literature survey and method development trials, it was determined that the analyte was unstable in plasma. Hence, further trials were taken by adding various concentrations of Ascorbic acid as stabilizing agent and it was determined that Rifampin and Desacetyl Rifampin were stable in 10 % of Ascorbic acid in Milli-Q-water. Consequently, the method development was performed with stabilized plasma. Results were provided in a soft copy.	

<table>
<tr><td colspan="2">Method validation: MV-077-01 and MV-077-02

Method validation for RIF and DES RIF took place in presence of INH.

The method validation was also applicable for application no study no. NCS-570-17-BA
In version MV-077-02 the Method validation of RIF and DESRIF was carried out in the presence of INH and ETH (Ethambutol HCL) and the upper range was increased.</td></tr>
<tr><td rowspan="2">The SOP for method validation was reviewed.

The Method validation plan/protocol was dated 3 Dec 2016.

Preparation of the calibration standards and QCs were reviewed and verified.</td><td>The Matrix factor was determined 3 Dec 2016

Specificity and selectivity was performed 3 Dec 2016 and the required numbers of lots (based on volume) were pooled for bulk spiking.

Dilution integrity for both RIF and DES RIF
2 x and 4 x dilutions were performed on 9 Dec 2016 and again 28 May 2017.
Acceptance criteria were met.

Carry over documentation dated 12 May 2017 was reviewed.
The blank analysed after the highest concentration 14 ug, showed no interference.</td></tr>
<tr><td>Precision and Accuracy</td><td>Six PA batches were run in four days.</td></tr>
<tr><td rowspan="2">Stability: Freshly spiked calibration curve and LQC and HQC for comparison were prepared.</td><td>Stock solution preparation documentation was provided and reviewed.</td></tr>
<tr><td>Freeze/Thaw
Rifampin and Desacetyl Rifampin in human plasma was demonstrated to be stable after 4 freeze/thaw cycles at about -70 °C.

The stability for LQC and HQC was established to be 102.83 % and 101.93 % for Rifampin and 99.75 % and 101.14 % for Desacetyl Rifampin respectively.</td></tr>
</table>

	Long term stability of analyte in matrix: Addendum I, dated 2 Aug 2017 for Long term stability and Specificity and selectivity was available. **Blood stability:** RIF and DES RIF were spiked one after the other both with fresh and stored stability sample (2 hour 15 minutes) however there was no difference in the results.
Back conversion	Not applicable.
Analysis of samples	
There was a total of 79 missing samples. Subject-wise sample verification form dated 23 Aug 2017 was reviewed and verified.	Randomly selected analytical runs were reviewed and verified. Same chromatographic parameters throughout the whole runs were confirmed. The process was adequately documented in the lab-notebook. ISD variation was checked and verified. The audit trail and runs were checked to verify that both files were the same and it was only an error in recording the name of the file. The retention time was updated to fit the chromatogram within their quantitation method.
Repeat analysis SOP for Repeat analysis of clinical samples defined the repetition of samples analysis in case the results fell above the calibration curve range. (Under code AC). The SOP was adequately descriptive. SOP for Handling of unexpected test results was also reviewed. More than 5 % samples were observed to be above ULOQ. The assessment of repetition of sample analyses and their impact on the integrity of results was reviewed and verified.	
Re-integrated chromatograms The blue area of chromatograms' area was automatically calculated by the software on the top of the chromatogram as Area (example 33625).	No re-integration of chromatograms was done in this study.

After running the analysis and creation of the chromatograms, all data was submitted to the designated QC-team. The QC-team investigated the quality of the chromatograms. In case of not acceptable chromatograms (for example chromatograms with split peak or when it had a merging peak) the analyst would be asked to re-integrate the chromatograms. Re-integration could be done either by changing the threshold area or smoothing factor. However, in case of merging peak, the analyst would use first the manual integration icon (on the top of the chromatograms) to calculate the area of merging. With manual re-integration, they had the option to cut the peak as desired. The excessive area would turn to white. If the remaining blue area was subtracted from the original blue area, the area could be calculated of the merging area. If this was more than 5 % of the peak of the interest, the chromatogram would be re-integrated.	
ISR The SOP for Investigation of high internal standard variability in subject samples was reviewed to verify the ISTD response area variation for all samples. The concentration obtained for the initial analysis and the concentration obtained by reanalysis should be within 20% of their mean for at least 67% of the ISR. It was noted that selection of the additional samples to be included in the ISR was in accordance with the ISR sample selection in the respective SOP. SOP for ISR was reviewed. The selection of additional samples was adequately described.	5 ISRs in 3 different days were run and the documentation was reviewed.

Study no:	**NCS-570-17-BA (Rifampin)**
Analysis of samples	
Randomly selected runs were verified, all adequately recorded and easily and readily retrieved. Arrangement of samples printed in hard copy and double checked prior to analysis. Samples loaded by analyst in accordance with applicable SOP. The acceptance criteria were met	
Re-integrated chromatograms	There were no re-integrated chromatograms.

Repeat analysis	31samples were repeated due to AC code (above Calibration curve, above ULLOQ). The reason was investigated in the report. The documentation for repeat analysis of sample dated 31 OCT 2017 was reviewed.
ISR	The procedure for the selection of additional ISR was adequately addressed in the SOP for incurred analysis which required compliance with both US and EU requirements, reflected as 7 and 10 % respectively. 67 % should be within 20 % of the mean, addressed in point 8.9 titled "ISR evaluation"
Back calculations	No back calculations were made as the instrument automatically provided all calculations.
Acceptable ranges fulfilled	Acceptance criteria were met.

Study no: **NCS-561-17**-BA	
Method validation: MVR-078-01-Isoniazid Method, also applicable for **study no. NCS-585-17-CS**	
Method validation consisted of three parts: • Main body • Addendum I for LT stability in plasma matrix • Addendum II for partial validation of the co-administrator drug - Ethambutol COAs were reviewed for all analytes and the pertaining Internal Standards.	**Matrix factor** The batch was prepared as the same batch together with the SPE-SEL batch. Documentation reviewed dated on 26 Dec 2016. The raw data and chromatogram results were reviewed and confirmed. **Selectivity** 6 plasma samples in addition to Lipemic and Haemolytic samples were provided and verified. The blank matrix was provided by the Pathological Laboratory on 30 Nov 2016. The samples were identified by assigning new batch no, to each of them. Preparation of stock solution and spiking solutions to make the samples (6 individual sources of blank matrix) was reviewed, dated 26 Dec 2016. The pertaining preparation of IS was also reviewed, prepared on the same day.

	All acceptance criteria were met. No interference was observed. **Dilution integrity** Preparation of dilution solutions as stock solution and spiked solutions was properly documented. The experiment was done together with FT4 on 4 Jan 2017 and met the acceptance criteria.
Precision and Accuracy	6 P&A was performed, in accordance with the applicable procedure, on three days with two different analyst/columns with same or different instrument of same model. All the batches met the acceptance criteria.
Stability: Freshly spiked calibration curve and LQC and HQC for comparison was provided.	**Freeze/Thaw** 4 cycles were provided together with the dilution integrity. The storage and retrieval of the samples for 4 periods for at least 12 hours and 24 hours storage was verified against the Freezer log. The checksum verification was reviewed. **Bench Top** The analytical run, together with Bench top storage and retrieval of the samples were properly carried out. **Long term stability stock solution** The analytical run was properly documented. Stock dilution form prepared on 02 DEC 2016 for the samples LTWS, also the IS was reviewed. Another IS solution was made on 2 Dec 2016 6 replicates of each sample were used. The preparation of AQSTD stock solution (6 replicates) was reviewed from the stock solution made on 2 Dec 2016 until 26 Dec 2016 (24 days) Freshly made AQSTD_FR_SOL: preparation was verified on the same day as 26 Dec 2016.

	Long term stability of analyte in matrix The preparation of fresh CC and QCs on 21 Mar 2017 was reviewed. Documentation for sample processing form was reviewed. The storage of samples LT-LQC and LT HQC 25 – 30 on 26 Dec 2016 and retrieval on 21 Mar 2017 removed at 2:36 pm was reviewed.

Study No	**NCS-561-17-BA**
ANALYTES	**Rifampin and Desacetyl-Rifampin and Isoniazid (INH)**
Analysis of samples Randomly selected analytical runs were reviewed. All were adequately recorded and easily and readily retrieved. The Arrangement of QC samples was printed in hard copy and double checked prior to analysis. The printing times, analyst loading times and run starting times were verified. Acceptance criteria were met.	
Repeat analyses documentation for RIF, DES RIF was reviewed and verified to be in accordance with the applicable SOP.	
Re-integrated chromatograms Allowable shift in RT should not be greater than 0.5 min of the pre-set criteria. Integration SOP: The sample analysis protocol for rifampicin provided the integration and identification parameters for the analysis of Rifampin and Desacetyl-Rifampin.	There were no re-integrated chromatograms
ISR	DES RIF 142 of 1278 samples 11,11 % No sample result was outside the limit - all met acceptance criteria.

	RIF 142 of 1278 samples 11,11 % 140 were within limit. 2 samples demonstrated BLQ and not considered for the calculation. All 140 sample results were met the acceptance criteria.
Back calculations	Not applicable.

Study no: NCS-585-17-CS (Rifampin and Isoniazid)	
Analysis of samples	
Missing samples were verified. Usage of Calibration standards was verified. System suitability for 13 Mar 2018 was reviewed and verified. Reconciliation of CCs and QCs for Isoniazid was reviewed. DI QC reconciliation was physically verified in the freezer. A total of 27 DI QC samples were prepared. None of them were used and all existed in the freezer. For this study, the stabilizer factor was used and hence the dilution factor was set up as 1.111 for the subject samples	Randomly selected sample analytical runs were reviewed.
Repeat analysis SOP for Repeat analysis of clinical samples of 28 Mar 2017 was applicable for this study. QCs were interspersed within the batch, using HQC, samples, MQC samples and LQC samples. 4 sets of QCs in each batch of 85 samples were used. Reconciliation was provided.	No repeats were performed for this study.

Re-integrated chromatograms	No re-integrated chromatograms were in this study. Manual re-integration was not allowed.
ISR	Number of sample used for ISR run was 136 out of 1021 samples for INH. 16, 24 and 48 hr samples were not included in analysis of the INH. ISR1 was performed on 24 Mar 2018. ISR2 and ISR3 were performed on 26 Mar 2018. ISR1 was randomly compared with the raw-data and the data reported in the report. ISR used 136 samples out of 1224 samples for Rifampin. All 6 ISRs met the acceptance criteria.
Back calculations	The back calculation was done by the software system. Accuracy was calculated by the software, followed by QA-team verification.
Acceptable ranges fulfilled	All of the batches for both Rifampin and INH met the acceptance criteria.

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

18. Sample collection, storage and handling of biological material

Collection of blood samples

The collection of blood from one of the volunteers was observed. Procedures were readily displayed at the centrifuge and on the wall where the nurse was positioned. An external laboratory was contracted to test the samples prior to the trial. The pathology reports were reviewed.

Three labels were prepared by the nurse during blood collection, one for the urine collection container and two for blood tubes.

The Service agreement between Norwich Clinical Services Private Limited and testing Pathology Laboratory was reviewed. The Agreement was dated and signed 17 Jan 2018. The Turnaround time for results was 6-8 hours for routine sample and 3-4 hours for urgent samples. Data transfer between the two sites was via email to the principal investigator who would then review the results.

The CRO had 2 refrigerated centrifuges; Thermo Scientific Heraeus Multifge X3-R centrifuge, providing temperature between -10 to 40 and rpm of up to 11000. Both were well maintained with maintenance records available. SOPs were available next to the instruments. Centrifuge buckets were clean and stored appropriately. A haemolysis chart was available on the wall beside the centrifuge for the recording of samples. Log books for all instruments were available, legible and all columns populated correctly.

Observations made in relation to the handling of biological materials were addressed in the CAPA plan provided by the CRO.

Receipt and Request of samples

Samples received from the clinical unit were transferred in a thermos-box, however, the shipments from other CROs would be equipped with a data logger.

Upon the receipt of the shipment, samples were counted and verified, records were kept in the freezer logbooks with adequate information.

Request of samples for analytical run purposes was provided by the laboratory assistant. Samples were withdrawn from the respective freezer by the custodian to be delivered to the laboratory for a second verification. Furthermore, four subjects per study would be verified by the QA-team per their procedures.

19. Data processing and documentation

Integration settings of the analytical runs were reviewed. Smoothing was kept the same throughout the runs.

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

Raw data were generally documented in a manner that enabled the traceability with respect to sample and equipment identification and time and date of activity and the respective delegate.

Logbooks were consistently used to record the activities and usage of equipment throughout the organization.

There was a system in place for the validation of data entry with entries being checked by a second person.

20. Good laboratory practices

The bioanalytical laboratory was located on the Ground floor.

The laboratory was equipped with two refrigerators for storage of working standards and stock solutions, also one -20 ºC freezer for storage of working standards required to be stored at lower temperature.

In the Deep-Freezer room, there were seven -20 ºC and four -70 ºC freezers, connected to digital thermometer and data logger of Delta system. Regular monthly check of alarms took place. The alarm was also tested by the inspection team. Notification was made and the custodian was informed by the security through the internal extension number.

Equipment and calibration

NCS had a mature system in place for the maintenance and calibration of equipment within both the clinical and analytical facility, including a Master list of equipment 2018 which was made available. There were separate maintenance schedules for the two facilities. There was a working process in place for equipment breakdown. The process was reviewed for the following equipment and found to adhere to the written procedure - Handling Equipment/Instrument Malfunction or Breakdown

- Balance (model number ML204/01)
- Refrigerated centrifuge
- LCMS/MS

NCS had a preventive maintenance schedule that included regular cleaning of freezers and internal check of pipettes (3 monthly).

Randomly selected calibration records were requested and reviewed. All records were available and met criteria.

Temperature mapping of freezers and refrigerators was performed by an external company and all refrigerators and freezers including some rooms when revalidated were also temperature mapped. The reports provided by the service provider also included calibration reports of the loggers used.

Randomly selected maintenance related documents were reviewed and verified.

Pharmacokinetic, statistical calculations and reporting section

21. Pharmacokinetic, statistical calculations

Randomization
The Randomisation list was requested by the Pharmacy and provided by the statistician with use of SAS software system, together with the Seed Number.

The Email for request of randomization list for study NCS-585-17-CS dated 28 Feb 2018 was provided.

The biostatistician used his own printer and checked before printing and therefore did not experience errors. Three hard copies were provided in a sealed envelope and the activity was logged in the dispatch logbook, sent to the pharmacy for acknowledgment.

Pharmacokinetic and statistical calculations
The Clinical database was locked after completion of study trial in the SDMRS and a message was received. The analytical data was extracted into WinNonlin software system. In addition, the request was sent to pharmacy for acquisition of randomization data. The CRC manager sent an email with clinical data for the actual time point of sample collection, together with the scheduled time point.

Prior to the running of the Pharmacokinetic parameters, a quality control of raw data was performed by two QC-staff to ensure that the randomization process was carried out properly. The documentation pertaining to study no. NCS-585-17-CS including the sampling time-deviation dated 27 Mar 2018 was provided.

22. Study report
Study reports were provided and used during the inspection to confirm compliance.

Miscellaneous	
Samples taken	Not applicable
Assessment of the CRO master file	CRO Master file, as well as the Quality Manual were provided and reviewed.
Annexes attached	Not applicable

Part 3	Conclusion

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

Clinical and Bioanalytical site
Norwich Clinical Services Pvt. Ltd
Ground and First floor, 147/F, 8th Main, 3rd Block
Koramangala
Bangalore - 560 034,
Karnataka, 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. 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".
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. 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

13. 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

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

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