World Health Organization
20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.who.int

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	TB174 TB202
Study number	[redacted]
Title of the study	[redacted]
Clinical Part of the study: Name and address of the organization	Semler Research Center Pvt. Ltd. Sharon Hospital Campus, 18, Tanmag Road, Vinayagampatti, Salem 636 008 Telephone: 0427-2404612,2404614 Fax: 0427-2404611
Bio-analytical laboratory: Name and address	Semler Research Center Pvt. Ltd. 75A, 15th Cross, I Phase J.P. Nagar, Bangalore 560078. Telephone: 080-26640681/82 Fax: 080-26640683
Date of inspection	12, 14, 15 and 16 July 2010

World Health Organization
20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.who.int

Part 2: Summary

General information about the site(s)

Semler, located in Salem and Bengaluru was inspected on the above-mentioned dates. The inspection included training of one inspector in the conduct of a GCP inspection. The clinical part of the study was conducted in Semler located in Salem, and the bio-analysis was done by the Semler bioanalytical facility located in Bengaluru.

History of WHO and/or regulatory agency inspections

This Prequalification Programme inspection was the first inspection conducted by the WHO at these sites.

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product. The inspection covered all the sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Inspected Areas

The inspection focused initially on TB 202 followed by inspection of data for TB174. The report is divided into three sections. Section 1 covers general aspects relating to both studies and the CRO, while section 2 focuses on TB202 and section 3 on TB174.

Section 1
After arrival, the inspectors introduced the CRO to PQ requirements and the process. This was followed by a more formal introduction of representatives and their responsibilities. The Director / COO of Semler then made a presentation of Semler and its activities. The inspectors were informed that the CRO was part of a larger American based company with a business strategy covering pharmaceutical development, BA/BE studies and clinical development. Semler performed about 10 studies in 2009, and 40 in the first six months of 2010.

The inspectors started the inspection by reviewing several documents as reflected below. After lunch, they walked through the facility and inspected the respective areas and selected documents in the areas relating to activities in each area.

Documents reviewed included:

Agreements
The inspectors reviewed the agreements between the sponsors and the CRO. Some observations were made to the contents of the agreements.

Organization chart
The organization chart of the clinical unit was reviewed as well as the job descriptions and CVs of selected key personnel. The latest approved organization chart was dated 8 July 2010 as new staff had joined recently.

20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.who.int

Lists of staff including contracted staff in 2008 and 2010 were presented.

CVs of staff reviewed included:

- Principle investigator (in Bangalore)
- Clinical Investigator
- Pharmacist

Training:
A training matrix was presented as well as the training matrix for individuals. The training record of the pharmacist was reviewed. The training matrix and record for 2007 was inspected (as the pharmacist joined the CRO in that year). It was noted that the training records were maintained, however, the training for dispensing, archiving and retrieval of drugs was marked "NA" as it was explained that the pharmacist prepared these SOPs.

Ethics Committee (IEC):
The IEC consisted of 9 persons. It was established in 2007. It was explained to the inspectors that the IEC was registered as a company. (Registration as such was not inspected). The IEC had a meeting once a week. The SOP of the IEC was inspected. The IEC had an office in Salem. It operated in accordance with an SOP. The CV of the Chairman was reviewed, as well as that of the housewife represented on the IEC.

Volunteer recruitment and enrolment:
Volunteer recruitment was done through advertising and by word-of-mouth. There were about 1100 volunteers in the "volunteer bank". The process of recruitment and enrolment was explained. The wording for the advertisement was approved by the IEC. An example of an advertisement that was placed in the news paper was inspected.

General screening:
Volunteers were sent for screening at the SKS hospital in Salem - after informed consent was obtained for this "general" screening. The general screening included obtaining medical history, a physical examination, ECG, blood tests and chest X ray. The validity period was 21 days for tests and 6 moths for the X ray.

Study specific tests:
Eligible volunteers (from general screening) were screened (study specific) on the day of check in for a study.

The clinical units were inspected. The inspectors walked through the facility and inspected some documents including SOPs, records, registers and certificates. Areas inspected included:

- Areas where volunteers were received and ICFs were completed / signed
- Housing areas I, II and III
- Dosing and sample collection room
- Canteen
- Sample preparation areas with centrifuges
- Deep freezer room
- Recreation area
- Intensive care units (2)

20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.who.int

- Pharmacy and dispensing room
- Change rooms
- IT room (CCTV monitoring)
- Security room

Documents inspected in the above mentioned areas included:

- Deep freezer logs (samples in and out; temperature records),
- sample transfer,
- calibration of sensors and centrifuges,
- alarm log for deep freezers

On the second day of the inspection, the inspectors reviewed documents:

- Insurance records
- Company registration (February 2006)
- Project plan for both studies
- DCGI approvals
- List of contracted staff in 2010 (there was none in 2008)
- Payments and bills of the IEC
- Line clearance SOP
- Data logger printout : transfer of samples from Salem to Bangalore for both studies
- CV of the Director of Quality Affairs
- CV of one staff member, and training records for 2009 and 2010

On the third day of the inspection, the inspectors proceeded to the bio-analytical laboratory where they inspected some areas and activities. This included:

- Sample preparation area
- Balance room
- Refrigerators for stock solution and references standards
- Instrument room (HPLC LC/MS/MS)

The calibration records of some selected instruments were checked and included pipette MP154. The temperature records for the refrigerator were reviewed. It was explained that a temperature mapping study was done (annually). The log books for the use of reference standards were inspected. The column use register was inspected as well as the SOP for washing and storage of columns. The procedure for waste management was discussed.
The inspectors then reviewed the documentation related to method development and method validation (see section 2).

World Health Organization
20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.who.int

2.1 PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

2.2 THE PROTOCOL

The Protocol was found in general to be acceptable.

2.3 PROTECTION OF TRIAL SUBJECTS

Acceptable. Some minor observations were made and are listed in the report below.

Protection of the volunteers was found to be acceptable, Helsinki declaration was followed, and informed consents were within the requirements.

2.4 RESPONSIBILITIES OF THE INVESTIGATOR

Responsibilities of the investigator were defined, selection of subjects were done in accordance with defined procedures. Subjects were properly informed; ICFs were signed by the volunteers. Local drug authority was accordingly informed about the study. The study protocol was reviewed and approved by the ethics committee. Adverse reactions were recorded. The Monitor performed a site audit during the trial period I and period II, an audit report was available.

Pharmaceutical products were handled appropriately.

The trial site had adequate premises.

Some minor observations were made and are listed in the report below.

5. RESPONSIBILITIES OF THE SPONSOR

The activity inspected was found to be in general, acceptable. The trial was performed in accordance with the protocol. Trial management and handling of data was properly carried out. Required standard procedures were available. Subjects received compensation in accordance with the protocol. Quality audits were performed; audit reports were available for inspection.

Some minor observations were made and are listed in the report below.

6. RESPONSIBILITIES OF THE MONITOR

Responsibilities of the monitor were specified in the contract between sponsor and CRO. Case report forms were appropriate. Although there was some monitoring of the study, this required attention (See observations below).

7. MONITORING OF SAFETY

20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.who.int

Subject safety was monitored, adverse events were reported and subjects received necessary treatment.

8. RECORD-KEEPING AND HANDLING OF DATA

Handling of data was considered acceptable. Some findings were made regarding appropriateness of the archiving activities. Study records were stored accordingly.

9. STATISTICS AND CALCULATIONS

Not inspected.

10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

Supply of products and storage of products as well as labelling and packaging were found in general to be acceptable. Dispensing was done in accordance with an SOP.
Some minor observations were made and are listed in the report below.

11. ROLE OF THE DRUG REGULATORY AUTHORITY

Acceptable.

12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

A quality assurance system was in place. Audits of clinical and bioanalytical parts were performed, audit reports were available for inspection.

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, the studies:

- B174: [redacted]

[redacted]

And

World Health Organization
20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111 – www.who.int

- TB202: [redacted]

Conducted at Semler Research Center Pvt. Ltd., Sharon Hospital Campus, 18, Tanmag Road, Vinayagampatti, Salem and Semler Research Center Pvt. Ltd., 75A, 15th Cross, I Phase J.P. Nagar, Bangalore, India were considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP.

All the non-compliances observed during the inspection that were listed in the full 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.

World Health Organization

20, AVENUE APPIA – CH-1211 GENEVA 27 – SWITZERLAND – TEL CENTRAL +41 22 791 2111 – FAX CENTRAL +41 22 791 3111
www.who.int

WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	[redacted]
Study number	
Title of the study	
Clinical facility: Name and address	Semler Research Center Pvt. Ltd. Sharon Hospital Campus, 18, Tanmag Road, Vinayagampatti, Salem - 636 008, India Telephone: 0427-2404612, 2404614. Fax: 0427-2404611
Bio-analytical laboratory: Name and address	Semler Research Center Pvt. Ltd. 75 A, 15th Cross, I Phase J.P. Nagar, Bangalore - 560078, India Telephone: 080-42627200 Fax: 080-26640683
Date of inspection	11- 15 July 2011

Part 2: Summary

The purpose of the inspection was to inspect the bio-equivalence study performed at Semler Research Center Pvt. Ltd (hereafter referred to as "Semler"), to assess compliance with GCP, GMP and GLP (as appropriate) and to verify the related source data for the above mentioned study.

General information about the site

Semler was located in the following three different locations:

Clinical facility
Semler Research Center Pvt. Ltd.
Sharon Hospital Campus,
18, Tanmag Road, Vinayagampatti,
Salem - 636 008.

Screening Facility
Semler Research Center Pvt. Ltd.
C/O SKS Hospital
3rd floor, 23 SKS Hospital Road
Alagapuram
Salem -636004.

Bioanalytical and statistical facility
Semler Research Center Pvt. Ltd.
75 A, 15th Cross, I Phase J.P. Nagar,
Bangalore - 560078.

Semler bioanalytical facility was inspected on 11-12 July 2011, clinical facility on 13-14 July 2011 and screening Facility on 15 July, 2011.

History of WHO and/or regulatory agency inspections

This site was preciously inspected by the WHO team 12, 14, 15 and 16 July 2010

Focus of the inspection

This inspection focused on the bio-equivalence study performed on behalf of the sponsor for the above mentioned product (TB 199). The inspection covered the relevant sections of the WHO GCP, GLP and related texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

General information

Protocol issue date was 21 October 2010.

IEC approval date was 26 October 2010.

The study clinic start date period I was 27.10.2010. End date period I was 29.10.2010.
The study clinic start date period II was 10.11.2010. End date period II was 12.11.2010.

The study BA part start and end dates were the following:

[redacted] 15.11.2010. (start) 10.12.2010. (end)
18.11.2010. (start) 16.12.2010. (end)
15.11.2011. (start) 20.12.2010. (end)

Summary of an audited PK status results was dated [redacted]

[redacted]	Number of subjects
Planned	36
Enrolled	36
Subject dosed in Period 1	36
Subject dosed in Period 2	33
No. of subjects withdrawn	0
No. of subjects dropped out	3
Completed	33
Adverse drug events	4
Deviations from the protocol	3

Blood withdrawal
A total of 23 (1x6 ml) blood samples were collected from each subject in each study period.

The pre-dose and post-dose samples up to 24 hours were collected via an indwelling cannula placed in an ante-cubital vein or one of the forearm veins.

Heparin-lock technique was used to prevent clotting of the blood in the indwelling cannula.

The collected blood was transferred immediately after collection in vacuum tubes containing anticoagulant (K2EDTA) in each period.

The total volume of blood drawn including the volume necessary for the laboratory tests and the volume of heparinized blood discarded before each blood draw was about 310 ml for each subject for the entire study.

Blood sample collection and processing was done under yellow monochromatic light as [redacted] and ascorbic acid solution used as the antioxidant are both light sensitive.

Subject monitoring
Subjects were monitored at 4, 6, 12 and 24 hours post dose in each period. In addition, vitals were recorded at the end of the study.

The subjects were asked regarding their well-being at regular intervals. Hematology and serum biochemistry investigations (except blood grouping and Rh typing) done at screening were repeated at the end of study. Adverse event monitoring was done throughout the study. For all dosed subjects ECG was recorded at the end of study and documented in ECG recording form (appendix 10).

Immediately prior to check-in of each period, all subjects were tested for alcohol in breath and for the presence of drugs of abuse in urine.

Inspected Areas and documents reviewed

On the first day inspectors visited:

- BA laboratory
- Sample preparation
- LSMS room
- Balance room
- Deep freezers room
- Archive

On the first and second day the inspectors reviewed various documents which included SOPs such as:

- SOP "Sample transfer to Bioanalytical laboratory"
- Freezer print outs from 10.11.2010 till 17.12.2010.
- Data Logger memory
- Qualification report of freezer .Qualification was carried out for loaded freezer and unloaded freezer. Report was audited and approved by QA
- SOP "Receipt, storage and usage of reference standards"
- Alarm log book deep-freezer
- SOP"Chain of Custody of Biological samples"
- Performance qualification for temperature maintenance using dry ice. Conclusion was made that samples can be maintained at a temperature below - 50 C for approximately 42 hours
- SOP "Operation, maintenance and Qualification of Ultra Low Temperature Freezer" Freezer Maintenance records were presented and reviewed
- SOP "Operation; maintenance and qualification of Micropipettes". Micropipettes Performance Qualification was carried out on weekly basis and three month basis. Micropipettes Performance Qualification weekly and tree monthly performance Qualification reports were presented and reviewed
- SOP "Chromatographic Acceptance Criteria and Reintegration criteria"
- SOP "Preparation of Calibration Curve and Quality Control Samples and Batch acceptance Criteria"

- Working standard logbook for [redacted]
- Maintenance logs of LCMS used for [redacted]
- Colum usage logs for LCMS
- SOP "Quality assurance department"
- SOP "Training and job responsibilities of quality assurance unit clinical personnel"
- SOP "Study specific audit report"
- Organization chart
- Job description and training records of the Study Director
- Method validation protocol of [redacted]
- SOP "System suitability"
- SOP "Re-assay of samples in bioanalytical laboratory for pharmacokinetic reasons"
- List of studies performed during 2010.
- SOP "[redacted] in LC-MS/MS using [redacted] as internal standard in human plasma"
- SOP "Estimation of [redacted] as an internal standard"
- SOP "Estimation of [redacted] in human plasma using [redacted] as an internal standard"
- SOP "Reassay of samples in the bioanalytical laboratory"
- Log book for samples in-out to the deep-freezer ULTF
- SOP "Obtaining blood samples"
- SOP "Sample transfer to bioanalytical laboratory"
- SOP "Operation, maintenance and qualification of ultra low temperature freezers"
- Records of shipment of samples from clinical to bioanalytical facility
- Records of calibration of data-loggers used during shipment
- SOP "Operation, maintenance and performance of qualification of wireless data monitor"
- Temperature records for freezer (clinical facility) for the time period of the study (manual and electronic)
- SOP "Line clearance for drug dispensing"
- SOP "Line clearance for drug administration"
- SOP "Check-in and check out of subjects"
- SOP "Study specific training and delegation"
- Job description and training records on the specific study for clinical research coordinator, pharmacist, principal investigator, phlebotomist, contracted medical doctor
- SOP "Randomization and blinding procedures"
- SOP "Clinical study protocol preparation, review and version control"
- SOP Adverse event recording and reporting"
- Concomitant medication log
- Adverse event logs during study
- SOP "Lebeling of vacutainers and vials"

- SOP "Operation, maintenance, and qualification of micropipettes"

The method validation protocols and final reports for all of the four substances [redacted], as well as protocol and report for the study [redacted], were signed by the study director and included a QA statement. Minor comments were made referred to the latter, listed in the report below. Method validation for rifampicin was reviewed and verified, including specificity, reinjection, dilution, precision, and carry over, accuracy, recovery, matrix effect, stability (bench top, auto-sampler, freeze-thaw, long-term, stock solution).

Relevant dates regarding study [redacted] were the following:
- Experimental starting date: 15/Nov/2010
- Experimental completion date: 20/Dec/2010
- Date when samples where collected: 27 – 29/Oct/2010 (period 1) 10-12/Nov/2010 (period 2)
- Date when samples where received: 12/Nov/2010
- Study completion date: 28/Dec/2010

Usage, maintenance and calibration logs for relevant study equipment were reviewed (LCMS, micropipettes, scales, deep-freezers). The inspectors also checked test item and internal standards weights, preparation of working standards and spiked calibration curve and QC samples records, certificates of analysis and chain of custody was reconstructed. Records generated during the receipt of samples were reviewed, as well as sample accountability and crosschecking versus study raw data.

Back calculation of around 1/3 of the subjects (13 out of 36) was performed; for all of the subjects recalculated, acceptance criteria for 100% of the calibration standards and QC samples, internal standard variation, run times of the analytical sequences and time spent by the samples at room temperature (time from retrieval from the deep-freezer until placement into the auto-injector) were verified. Calculated concentrations were checked against concentrations indicated on chromatograms and the reported tabulated data and dossier report. Repeated analysis and missing samples were verified as well as the audit trail for their respective runs. Raw chromatograms of repeated analysis as well as from a number of subjects were checked.

<u>On the third day inspectors visited Clinical facility and screening facility.</u>

<u>The Clinical facility</u> was separated from the functional hospital.
The following activities and services were provided at the Clinical facility:
- Checking of volunteers for the studies
- Drug administration
- Blood sampling
  There were 8 phlebotomy stations and 8 phlebotomists available
- Sample storage
  There were three housing areas in total 48 beds were provided for the studies:

Housing area I had 12 beds
Housing area II had 12 beds
Housing area III had 24 beds

- Subject pantry area
- Two Intensive Care Units (ICU) with the following equipment were available for the studies
  - Deliberator
  - Pulso-meter
  - Suction equipment
  - ECG
  - Oxygen generator
  - Nebulizer
  - Cardio-monitor
  - Intubation bags
  - Essential medicines. On spot checks all medicines were within their shelf lives. Medicines inventory showing expiry dates was available and was kept up-dated. Till the date of inspection there were no subjects moved to the ICUs.
- One mobile ambulance
- Check out of volunteers
- Pharmacy, dispensing

Dieticians' service, preparation of food was outsourced; canteen was audited and approved by the Semler staff.

Volunteer recruitment and enrollment:
Volunteer recruitment was done through advertising and by word-of-mouth and recall from the data base. There were about 2463 volunteers in the "volunteer bank". In case advertising was done via newspaper, the IEC had to be informed and approval should be obtained

General screening:
Volunteers were sent for screening at the SKS hospital in Salem. The rooms provided for screening were separated from the hospital and entrance was controlled. The following activities and services were provided at the Screening facility:

- **Screening-enrolment.** Volunteers were assigned 6 digits identification number which will last for the entire subject "volunteer life". Volunteers had to sign written consent for enrolment, if necessary witness was present and also signed the form. Upon arrival volunteers had to register and they were given a token number. Upon arrival volunteer photo was taken and compared with photo (saved in the system) and ID number. Volunteers' data were stored on excel sheet, which was not validated. Only cross checks of date was carried out. CRO was in progress of introducing fingerprint identifications. Volunteers' last participation (data of last blood withdrawal) in the study was extracted from the excel sheet where it was entered manually. Excel sheet was passport protected.

- **Screening consent form.** Screening consent forms were given to the volunteers. If required, a witness was present. The following vital parameters were checked:
    - Weight
    - Height
    - Blood pressure
    - Temperature
    - Respiration rate
    - Pulse rate
    - ECG
    - Blood analysis (contracted to the hospital)
    - Urine analysis (contracted to the hospital)
    - X rays (contracted to the hospital)

The validity period was 21 days for tests and 6 moths for the X ray.

On the fourth day inspectors reviewed below listed documents and did some cross checks as mentioned below.

Ethics Committee (IEC)

The IEC consisted of 9 persons. It was established in 2007. The IEC had an office in Salem. It operated in accordance with a SOP . SOP specified:

- Training
- Responsibilities
- Functions
- Operations
- Meetings
- Hierarchy, etc

The following documentation was sent to the IEC on 21.10.2010 for review and approval

- Study protocol and appendixes'
- Declaration of sponsor
- Declaration of investigator
- Declaration of Helsinki
- Table of study meals
- Lab reference ranges
- Height and weight reference chart
- CV of investigators
- Sample CRF
- Restriction and well being questionnaire
- Inclusion and exclusion criteria form
- ECG recording form
- IC documents in English
- IC documents in Tamil

The following documents also were reviewed:

- ICF shipping letter to the ICE, sent 21.10.2010.
- Minutes of IEC meeting held on 26.20.2010.
- Confidentiality agreement with IEC was presented during inspection.
- IEC chairman CV and training
- IEC member secretary CV and training
- EC member CV and training
- Insurance, dated 11.12.2009. - which was valid for one year
- Pre screening information

Investigators brochure was not available. - Pharmacology section was part of the protocol and included:

- Mechanism of action
- Indications
- Dosing information
- Contraindications
- Pharmacokinetics
- Distribution
- Metabolism
- Elimination
- Warnings and precautions
- Drug interactions
- Adverse reactions
- Over dosage
- Parameters.

Protocol:

Protocol was issued on 21.10.2010 and approved by IEC 26.10.2010. The following documents were reviewed:

- ICF for screening - English and Gujarati languages
- ICF for study - approved by IEC English and Gujarati languages
- ICF for all subjects (signatures were cross checked with subject arrival records - ID)
- Enrolment forms were cross checked for all subjects:
- VIN (Volunteer Identification Number)
- initials
- signatures
- date of birth was verified as well as identification
- Screening consent forms for all subjects were crosschecked with VIN and signature list
- CRF for all subjects were reviewed and crosschecked with randomization list and drug administration labels:
- Screening records were filed separately from CRFs. Screening records for all subjects were reviewed and crosschecked (ECGs and Chest X rays). Also several other subject analysis were cross checked.

- Vacutainer labels
- Break-up compensation policy approved by IEC on 4.3.2010.
- Compensation list and payment slip
- Insurance policy

Other documents reviewed:

- Study specific delegation training and signature log
- Study specific training document
- QA audits were carried out in accordance with the SOP"Study specific audit in the clinical unit" .Audits were carried out at specific time periods as:
    - Pre-study
    - During study
    - After study

Check lists were used for the audits. During the check list review observations had been raised. Responses were given in conservation response sheets. Responses were verified by the QA department staff. After that the QA statement has been issued.

Temperature records for the time period of the study (manual and electronic) were reviewed, as well as temperature recorded during the shipment of the samples to the bioanalytical facility were reviewed. Line clearance for drug dispensing for period I and period II, as well as line clearance for drug administration for period I and II were checked.

It was also verified the concomitant medication log, and adverse event log for the study; furthermore, job description and training records for the pharmacist, principal investigator, phlebotomist and contracted medical doctor were reviewed. Electronic backups were made on a daily, weekly and monthly basis; at the end of the month, a full copy was sent to an external facility. Integrity of information upon retrieval has been tested during periodic mock-ups.

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

Acceptable

2.2. THE PROTOCOL

The Protocol was found in general to be acceptable. Following deviations were recorded:

- Blood sampling deviations
- One subjects did not turn up for the end lf study safety analysis
- Check in deviations

2.3. PROTECTION OF TRIAL SUBJECTS

Protection of the volunteers was found to be acceptable, Helsinki declaration was followed, and informed consents were within the requirements.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

Responsibilities of the investigator were defined, selection of subjects were done in accordance with defined procedures. Subjects were properly informed; ICF's were signed by the volunteers. Adverse reactions were reported. The study protocol was reviewed and approved by the ethics committee. The Monitor performed a site audit and monitoring reports were available.

Pharmaceutical products were handled appropriately. The trial site had adequate premises.

2.5. RESPONSIBILITIES OF THE SPONSOR

The activity inspected was found to be in general, acceptable. The trial was performed in accordance with the protocol. Trial management and handling of data was properly carried out. Required standard procedures were available. Subjects received compensation in accordance with the protocol.

2.6. RESPONSIBILITIES OF THE MONITOR

Responsibilities of the monitor were specified in the contract between sponsor and CRO. Case report forms were appropriate. Although there was one monitoring visit carried out of the study, this required attention (See observations below).

Monitor report was dated October 27.2010. Monitor carried out only one visit before the study. Monitor report was available as a check list, covering:

- Protocol
- Study personnel records
- Screening
- ICF
- Clinical supplies receipt/dispensing accountability
- Dispensing & dosing of clinical supplies
- Phlebotomy
- Subject CRF
- Documentation Standards
- QA

2.7. MONITORING OF SAFETY

Subjects were monitored for safety and tolerability during the study and until the completion of the study. Safety assessments were done based on clinical observations, laboratory data at the beginning and at the end of the study and evaluation of the AEs observed during the course of the study. Adverse drug events were classified as:

- Mild
- Moderate
- Severe

Four Adverse Drug Reactions were reported and classified as mild and unlikely related to the study.

2.8. RECORD-KEEPING AND HANDLING OF DATA

Handling of data was considered acceptable. Study records were stored in the CRO archive.

2.9. STATISTICS AND CALCULATIONS

Not inspected

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

Supply of products and storage of products as well as labeling and packaging were found in general to be acceptable. Dispensing was done in accordance with an SOP.

The following documentation for investigational products was reviewed:

- Courier slip for shipment of IMP
- Gate pass documents:
  - Covering letter dated
  - CoA [redacted]
  - CoA [redacted]
  - CoA [redacted]
  - Data logger print outs
  - Import license for [redacted]
  - Purchase invoice f[redacted]

Drug product reconciliation was carried out - no deviations were observed.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

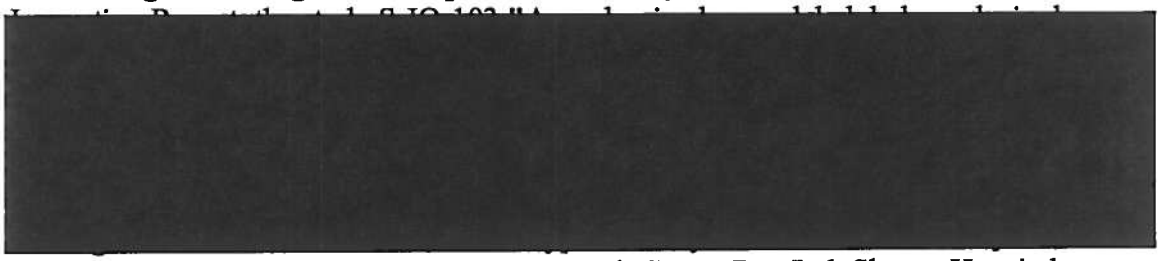
Acceptable

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

A quality assurance system was in place. Audits of clinical and bioanalytical parts were performed, audit reports were available for inspection,

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



fasting conditions conducted at Semler Research Center Pvt. Ltd. Sharon Hospital Campus, 18, Tanmag Road, Vinayagampatti, Salem - 636 008, Semler Research Center Pvt. Ltd. C/O SKS Hospital 3rd floor, 23 SKS Hospital Road Alagapuram Salem -636004 and at Semler Research Center Pvt. Ltd. 75 A, 15th Cross, I Phase J.P. Nagar, Bangalore - 560078 was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP.

All the non-compliances observed during the inspection that were listed in the full 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.

20, avenue Appia – CH-1211 Geneva 27 – Switzerland – Tel central +41 22 791 2111 – Fax central +41 22 791 3111
www.who.int

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	HA549 and MA099
Study number	[redacted]
Title of the study	[redacted]
Clinical Part of the study: Name and address of the organization	Semler Research Center Private Limited P A Arcade, No 21, 22, 23 Kodigehalli Main Road Sahakarnagar Bangalore-560092 Tel 080-43027100
Bio-analytical laboratory: Name and address	Semler Research Center Pvt. Ltd. 75A, 15th cross, I Phase, JP Nagar, Bangalore-560078 Telephone: 080-42627200, Fax: 080-26640683
Date of inspection	25 to 28 March 2013

Part 2: Summary

General information about the site(s)

Semler Research Center (SRC) is part of US based Arnold A Semler Inc, in business since 1946. SRC was founded in 2006, is a privately owned pharmaceutical services company with its business offices in Los Angeles, CA and Bangalore, India. SRC provides wide services primarily in the areas of pharmaceutical development, bioavailability and bioequivalence studies, early and late phase clinical development, regulatory services and medical & scientific writing. SRC employs 190 people.

The corporate office is located at J.P. Nagar, Bangalore, Karnataka where opening meeting took place. The bioanalytical facility is located at 2nd floor of the corporate office and is spread over about 7000 sq. ft. The facility has demarked to support the smooth flow of activities such as, access controlled sample storage area, sample processing room, balance room, washing room and Instrumentation room.

Bangalore clinical facility is located at Kodigehalli, Bangalore, Karnataka. The facility is about 20,000 sq. Ft area spread over 3 storey building. Clinical facility is 72 bedded (24+24+24) for BA/BE divided into 3 different wards along with the well-equipped intensive care units (2 beds divided into 2 units). The clinical research centre is clearly demarked as per the activities such as volunteer screening area, counselling area, in-house clinical testing laboratory, volunteer housing area along with the wash rooms, Investigational Products (IPs) administration area, phlebotomy (sample collection and processing area), access controlled pharmacy, recreation area and dining rooms for the study volunteers.

History of WHO and/or regulatory agency inspections

- Drug Controller General of India (DCGI) approval in 2011
- WHO Geneva inspection in 2010 and 2011
- USFDA inspected in May and September 2012

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the products, [redacted] (MA099) and [redacted] (HA549). The inspection covered all the sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Inspected Areas

A. BIOANALYTICAL PART

1. Overview and brief visit of facilities and equipment
2. Management of computerized systems and protection of data (verification of documentation vs. practice)
3. Review of source data in electronic and hard copy (Sample analysis for Period I and Period II)
   - Back calculations
   - Acceptability of runs
   - Review of source data (Preparation of matrix, stock, QCs and stability (weighing, calculations, and chromatograms, method development and validation)
4. Reanalyses, repeat analyses, ISR
5. Bio-analytical Method development
6. Bio-analytical Method validation data
   - SOP
   - Protocol and report
   - Precision, accuracy etc.
7. Plasma selection and pooling
8. Stock solution preparation
   - QCs
9. Stability data (stock solution and samples)
   - Short term
   - Long term
   - Freeze thaw
   - In injector/Autosampler
10. Laboratory inspection
    - Instruments and equipment
    - Pipettes
    - Sample management
    - Deep freezers
    - Reference standards
    - Fridges

B. CLINICAL PART

1. Overview of clinical part presentation
2. Physical tour of clinical area including:
   - Registration (this will include an examination of the databases in use and means of retaining information on subjects)
   - Screening (instruments used)
   - subject change rooms
   - CPU
   - ICU
   - Pathology laboratory

- Pharmacy

3. Documentation review
   - Contract between Sponsor and investigator
   - Review of Sponsor responsibilities
   - Review of CRO responsibilities
   - Principle Investigator and staff involved in the study
   - Review of Ethics Committee composition, responsibilities, SOPs, detailed minutes of meetings discussing the study under review
   - Review of Protocol, volunteers, ICF, Screening and CRFs
   - Verification of Source data
   - QA Audit reports
   - Monitor reports
   - Randomization
4. Pharmacy and investigational products
   - Site inspection. CPU
   - Dosing
   - Storage
   - Reconciliation of IPs
   - Line clearance procedures and documentation.
5. Sample collection, preparation and storage
   - Visit of applicable areas and of refrigerators, deep freezers and ultra-deep freezers in use
   - Qualification and performance verification of equipment.
6. Archives (paper and electronic)
   - Access control
   - Document traceability
   - Protection of documentation and
   - Statistical analysis

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

This part of the trials was found to be satisfactory overall for the studies examined and for the facilities. The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.2.THE PROTOCOL

For the studies that were seen, protocols were considered to be acceptable overall.

2.3. PROTECTION OF TRIAL SUBJECTS

Although most of the elements were fulfilled, some issues of concern were found during the inspection which had been addressed adequately. This will be verified during the next inspection.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

The curriculum vitae of the principal investigator and co-investigator confirmed their adequate qualification and competency in Good Clinical Practices. The assigned investigator was responsible for the recruiting of suitable subjects based on the inclusion and exclusion criteria. The information given in the protocol was communicated to subjects before the start of the BE studies.

The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.5. RESPONSIBILITIES OF THE SPONSOR

The observations raised pertaining to the inadequate responsibility of the sponsor had been adequately addressed, and the same shall be verified during the next inspection.

2.6. RESPONSIBILITIES OF THE MONITOR

The observations raised pertaining to the inadequate monitoring had been adequately addressed, and the same shall be verified during the next inspection.

2.7. MONITORING OF SAFETY

The subjects were assessed before the entry of subjects into study as per the selection and withdrawal criteria stated in the protocol. The vital signs and clinical examination were conducted as per the protocol. Also, the protocol required handling and reporting of adverse events and serious adverse events. In general, this area was found satisfactory.

2.8. RECORD-KEEPING AND HANDLING OF DATA

The archives and electronic records were found to be acceptable overall.

2.9. STATISTICS AND CALCULATIONS

Methods of communicating the information between bioanalytical and the Pharmacokinetics/Biostatistics (PB) department were verified briefly. Statistics and calculations were performed by a biostatistician located at the J.P. Nagar in Bangalore. In general, this area was found satisfactory.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

The test and reference quantities were verified and found to be satisfactory. The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

The facility had been approved by the Central Drugs Standard Control Organization (CDSCO). An observer from the CDSCO was present and observed the WHO inspection.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

This area was generally satisfactory. The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

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 *HA549* and *MA099* was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at Semler Research Centre (SRC) at JP Nagar (bioanalytical) and PA Arcade, Sahakarnagar (clinical), Bangalore, India.

All the non-compliances observed during the inspection that were listed in the full 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.