

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)**

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	TB174 TB202
Study number	TB174: S-10-007 TB202: S-08-010
Title of the study	TB174: S-10-007 A randomized, open label, balanced, single center, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Isoniazid 300 mg tablets (TB174) and Isoniazid tablets USP (Isoniazid) 300 mg (reference) in healthy human adult subjects, under fasting conditions.
	TB202: S-08-010 An open label, balanced, randomized, single center, two treatment, two period, two sequence, single dose, crossover bioequivalence study of two tablets of fixed dose combination each containing Rifampicin 150 mg + Isoniazid 75 mg (TB202) and one tablet of RIFINAH [®] (fixed dose combination containing Rifampicin 300 mg + Isoniazid 150mg) (reference) in healthy, adult, human subjects, under fasting conditions.
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, 15 th 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

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.



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 months 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)



- 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).

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



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: S-10-007

A randomized, open label, balanced, single center, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Isoniazid 300 mg tablets (TB174) and Isoniazid tablets USP (Isoniazid) 300 mg (Innovator) in healthy human adult subjects, under fasting conditions;

And



- TB202: S-08-010

An open label, balanced, randomized, single center, two treatment, two period, two sequence, single dose, crossover bioequivalence study of two tablets of fixed dose combination each containing Rifampicin 150 mg + Isoniazid 75 mg (TB202) and one tablet of a fixed dose combination containing Rifampicin 300 mg + Isoniazid 150mg (Innovator) in healthy, adult, human subjects, under fasting conditions

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.