

**WHO PUBLIC INSPECTION REPORT
(WHOPIR)
Contract Research Organization**

Part 1: General information

WHO product number covered by the inspection	TB 193
Study number	BBRC/EX/10/005
Title of the Study	A bioequivalence study comparing Fixed Dose Combination (FDC) of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol Hydrochloride Tablet (containing Rifampicin 150 mg, Isoniazid 75 mg, Pyrazinamide 400 mg and Ethambutol Hydrochloride 275 mg) of Svizera Labs Pvt. Ltd., Mumbai, India with Rimactan® 150 Capsules (containing Rifampicin 150 mg) of Sandoz Pharmaceuticals AG, Steinhausen; Isozid® 100 mg Tablet (containing Isoniazid 100 mg) Fatol; Pyrazinamid "Lederle" Tablet (containing Pyrazinamide 500 mg) of RIEMSER Arzneimittel AG and Myambutol® 400 mg Tablet (containing Ethambutol Hydrochloride 400 mg) of RIEMSER Arzneimittel AG, in 32 healthy adult human male subjects under fasting condition.
Clinical part of the study Name and address of the organization	Bombay Bioresearch Centre (BBRC) Plot N° 35, Deonar Ancillary Industrial Plots, Govandi, Mumbai - 400 043, India
Bioanalytical laboratory Name and address	Bombay Bioresearch Centre (BBRC) Plot N° 35, Deonar Ancillary Industrial Plots, Govandi, Mumbai - 400 043, India
Dates of inspections	18 - 20 July 2011

Part 2: Summary

The CRO Bombay Bioresearch Centre (hereafter referred to as BBRC) located in Mumbai, India, was inspected by a WHO prequalification inspection team on the above mentioned dates.

History of inspections - (WHO, regulatory authorities etc.)

This CRO was previously inspected in January and April 2008 and in June-July 2009 by teams of inspectors from WHO. This was the sixth WHO inspection at this site. The inspection in 2009 resulted in a Notice of Concern being issued to the site by the WHO on 21 July 2009.

Another GCP inspection was done on 11 - 15 October 2010 which resulted in the lifting of the NOC. The last WHO inspection was carried out on 18-20.05.2011. The conclusion was made that the clinical part of that specific study inspected was carried out in compliance with WHO guidelines.

The site is authorized by the Indian regulatory authorities.

The site was also previously inspected by the following National Drug Regulatory Authorities:

- MCC (South Africa)
- AGES (Austria)
- ANVISA (Brazil)
- FDA (USA)
- MHRA (UK)
- DCGI (India).

Purpose of the inspection

The purpose of the inspection was to verify the quality and integrity of the data and information for a bioequivalence study report submitted by the sponsor to the WHO, and to assess whether the study was conducted in compliance with the protocol, Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

Focus of the inspection

The inspection focused on the following product in the WHO prequalification pipeline:

- **TB 193:** This study was added to the inspection schedule one day before the inspection. Because of that inspectors did not have available data to prepare for inspection. Study related data were presented during inspection by the CRO. Most, if not all the staff that carried out this particular bioanalytical study, had already left the organization by the time of the inspection. Explanation regarding study was provided to the inspectors by the staff that did not take part in the study but was familiar with the study. Inspectors received notice from assessors one day before the inspection that there could be possible problems with the study (assessors observed high variations in the range of the slopes of the calibration curves). Therefore the inspection focused only on this study and extensive verification was done, especially on bioanalytical part of the study.

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. Particular attention was paid to the Bioanalytical (BA) part of the study. The inspectors reviewed the raw data and data stored in the software. The inspectors crosschecked the data (hard copies versus electronic data).

General information about studies

Study code: BBRC/EX/10/005 (TB 193)

Study title

A bioequivalence study comparing Fixed Dose Combination (FDC) of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol Hydrochloride Tablet (containing Rifampicin 150 mg, Isoniazid 75 mg, Pyrazinamide 400 mg and Ethambutol Hydrochloride 275 mg) of Svizera Labs Pvt. Ltd., Mumbai, India with Rimactan[®] 150 Capsules (containing Rifampicin 150 mg) of Sandoz Pharmaceuticals AG, Steinhausen; Isozid[®] 100 mg Tablet (containing Isoniazid 100 mg) Fatol; Pyrazinamid "Lederle" Tablet (containing Pyrazinamide 500 mg) of RIEMSER Arzneimittel AG and Myambutol[®] 400 mg Tablet (containing Ethambutol Hydrochloride 400 mg) of RIEMSER Arzneimittel AG, in 32 healthy adult human male subjects under fasting condition.

Study Initiation Date (Period I): 20th August, 2010 (First dosing date)

Study Completion Date (Period II): 29th August 2010 (Last sampling date)



Study period: Duration of the Clinical Phase	
Date of First enrolment: 20 th August, 2010	
Date of Last sample: 29 th August 2010	
Bio-Analytical Phase: Duration of the Bio-Analytical Phase	
Rifampicin, its metabolite, Isoniazid	Ethambutol and Pyrazinamide
Initiation Date : 09 th September, 2010	13 th September, 2010
Completion Date : 27 th September, 2010	25 th September, 2010

Inspected Areas and documents reviewed

Methods validation

Rifampicin, its metabolite, Isoniazid	Ethambutol and Pyrazinamide
Initiation Date : 23 rd July, 2010	06 th September, 2010
Completion Date : 27 th August, 2010	26 th October, 2010

Study design: Open label, randomized, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study in healthy adult human male subjects under fasting conditions.

Study Plan: Subjects were confined to clinical pharmacological unit about 12-20 hours prior to dosing till 24 hours post dose on two occasions after washout period of 6 days between two periods. Subjects were under fasting condition for at least 10 hours prior to dosing. Standardized meals were provided to the subjects at 4, 8 and 13 hours after dosing. A total no. of 22 venous blood samples were withdrawn. The actual collection time of each blood sample was noted accurately.

Drinking water was restricted for subjects from 1 hour pre-dose until 2 hours post dose. Vital signs like axillary temperature, respiratory rate, blood pressure, and pulse rate were measured during screening, on the pre-study day and at 0.00 (pre-dose), 1.00, 3.00, 6.00, 11.00, 24.00, 48.00 and 72.00 hours post dose during each study period.

Total 56 subjects were screened, out of which 36 subjects were reported fit as per inclusion, exclusion criteria. 32 subjects were recruited in the study. Bio-analysis of plasma samples of all completed subjects was done and data was reported on total 32 completed subjects.

	Number of subjects
Planned	32
Enrolled	32
Subject dosed in Period I	32
Subject dosed in Period II	32
No. of subjects withdrawn	N/A
No. of subjects dropped out	N/A



Completed	32
Adverse drug events	02 - possibly related to the products
Deviations from the protocol	Time point deviations Period I and Period II Vitals deviations during Period I and II

Date of Report was: 01st April, 2011

Clinical part

Documentation reviewed during inspection included:

1. Independent ethics committee documentation
2. Contract between sponsor and CRO
3. Screening, and study consent forms
4. Source data and results (lab results, ECGs)
5. Documentation and SOPs relating to study drugs (see details *) accountability, proof of purchase (missing), shipping, delivery, dispensing, line clearance form dosing records, and study drug labels
6. Randomization schedule (SAS software vs dosing form)
7. Study drug administration
8. Blood sample collection
9. Lists of staff present during the study
10. CRF's subjects No 01, 03 and 07 to 09 were crosschecked
11. Monitoring report
12. Blood samples storage condition and accountability
13. Reconciliation and checks of remaining medicines were carried out in the Pharmacy department. No comments were made.

Total 32 healthy adult human male subjects who met all inclusion and exclusion criteria were enrolled in the study. All the subjects completed both periods of the study.

The dosing labels were not the part of the CRFs. CRFs only mentioned T (test product and R (reference product).

Original test results as for example blood and urine analysis were kept separately from the CRFs.

Randomization schedule was crosschecked for all subjects and both periods.

Bio-analytical part:

Documentation reviewed during inspection included:

Two methods validation were used for all products

1. **Method Validation for the Determination of Pyrazinamide & Ethambutol** from Human Plasma by LC-MS/MS using Sulphamethoxazole as an Internal Standard.
2. Annexure to Method Validation Report BBRC/BAL/MVR/111 to **Method Validation for the Determination of Pyrazinamide & Ethambutol** from Human Plasma by LC-MS/MS using Sulphamethoxazole as an Internal Standard.

3. **Method Validation for the Determination of Isoniazid; Rifampicin & 25 - Desacetyl Rifampicin** for human Plasma by LC-MS/MS using sulphamethoxazole as an Internal Standard.
4. Annexure to Method Validation Report BBRC/BAL/MVR/110 to **Method Validation for the Determination of Isoniazid; Rifampicin & 25 - Desacetyl Rifampicin** for human Plasma by LC-MS/MS using sulphamethoxazole as an Internal Standard.
5. Annexure to Method Validation Report to **Method Validation for the Determination of Isoniazid; Rifampicin & 25 - Desacetyl Rifampicin** for human Plasma by LC-MS/MS using sulphamethoxazole as an Internal Standard.

For both method validations, preparation of stock solution, CCs and QCs (weighings, dilutions, COA's) were checked with back calculations.

For stability experiments (LT and Freeze thaw), preparation of fresh CCs, was checked, for precision and accuracy some QCs were back-calculated, selectivity was checked. Those raw data were checked vs final report.

SOP "Batch acceptance criteria for method validation and subject sample analysis and investigation report for batch failure" was reviewed, no comments were made.

Subject sample analysis

Rifampicin, its metabolite, Isoniazid	Ethambutol and Pyrazinamide
Initiation Date : 09 th September, 2010	13 th September, 2010
Completion Date : 27 th September, 2010	25 th September, 2010

The following data were crosschecked:

Preparation of stock solution used for preparation of CCs and QCs for all (5) analytes: back calculation of concentrations and dilution, quantity prepared (enough for approx for 40 runs for each method, only the half was used). A few other stock solutions were prepared for system suitability tests.

Excel sheet was designed during inspection for back calculation of QC's, and subject sample concentration: no significant differences were observed. The CD with the Excel sheet will be sent for review to WHO assessors.

Area ratio for some QCs was checked (for subjects 01 to 06 for Ethambutol & Pyrazinamid).

Raw data versus report for:

- QCs for subjects 01 to 06 for Ethambutol & Pyrazinamid.
- QCs for subjects 15, 16, 31, 32 for Rifampicin, Isoniazid, 25-desacetyl rifampicin.

Electronic files versus report for:

- QCs values for subjects 01 to 06 and 10 to 12 for Ethambutol & Pyrazinamid.
- Excluded CCs for all run for Ethambutol & Pyrazinamid.

- Sample subject concentration and failed QCs for Rifampicin, Isoniazid, 25-desacetyl rifampicin for subjects: 13, 15, 18, and 31.

On electronic files, CCs and QCs acceptance criteria for:

- Subjects 01 to 06 and 10 to 12 for Ethambutol & Pyrazinamid.
- Subjects : 13, 15, 18, 31 for Rifampicin, Isoniazid, 25-desacetyl rifampicin
- Logbook of LCMS MS used (n° 102 & 103) for the analysis (one dedicated to each method).

Audit trail for subject samples:

- 04 to 06 for Ethambutol & Pyrazinamid.
- 13, 15, 17 to 19 for Rifampicin, Isoniazid, 25-desacetyl rifampicin.

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

Acceptable

2.2. THE PROTOCOL

The Protocol was found in general to be acceptable.

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. 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

Staff with appropriate qualification and experience was involved in the study. Case report forms were not completely appropriate as dosing documentation was kept on a separate form.

2.7. MONITORING OF SAFETY

Subjects were monitored for safety and tolerability during the study and until the completion of the study.

There were 2 AEs reported: both AEs possibly were related to the products

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 labelling and packaging were found in general to be acceptable. Dispensing documentation was sufficiently detailed. The following documents were checked related to the tests and reference products:

- CoA for all products
- Commercial invoice for Rimactan
- Commercial invoice for Isozid
- Commercial invoice for Myambutol
- Commercial invoice for Pyrazinamid "Lederle"
- Svizera letter 07/08/2010 regarding sending WHO reference samples
- Svizera letter 18/08/2010 regarding sending test samples
- CoA (Svizera) Rifampicin API
- CoA (Svizera) Isoniazid API
- CoA (Svizera) Ethambutol HCL
- CoA (Svizera) Pyrazinamide API
- GMP Certificate (issued by the FDA Maharashtra State)
- Form 26 Certificate of Renewal of License
- Temperature data logger chart
- DHL shipment details for Pyrazinamid "Lederle"
- Prove of purchase of Pyrazinamid 500 mg tablets, Rimactan 150 mg capsules, Isozid 100 mg tablets and Myambutol 400 mg tablets

Re-conciliation of test products and investigational products was carried out on the third day of the inspection. No comments were made by inspectors. Investigational and test products were stored properly and re-calculation showed the right results.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

Acceptable

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

The quality assurance was consistent and acceptable.

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 **Study No BBRC/EX/10/005 Title: A bioequivalence study comparing Fixed Dose Combination (FDC) of Rifampicin, Isoniazid, Pyrazinamide and Ethambutol Hydrochloride Tablet (containing Rifampicin 150 mg, Isoniazid 75 mg, Pyrazinamide 400 mg and Ethambutol Hydrochloride 275 mg) of Svizera Labs Pvt. Ltd., Mumbai, India with Rimactan® 150 Capsules (containing Rifampicin 150 mg) of Sandoz Pharmaceuticals AG, Steinhausen; Isozid® 100 mg Tablet (containing Isoniazid 100 mg) Fatol; Pyrazinamid "Lederle" Tablet (containing Pyrazinamide 500 mg) of RIEMSER Arzneimittel AG and Myambutol® 400 mg Tablet (containing Ethambutol Hydrochloride 400 mg) of RIEMSER Arzneimittel AG, in 32 healthy adult human male subjects under fasting condition conducted at Bombay Bioresearch Centre (BBRC) Plot N° 35, Deonar Ancillary Industrial Plots, Govandi, Mumbai - 400 043, India 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.