



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	TB189 Rifampicin/isoniazid 150/75mg tablet
Study number	No. BBRC/EX/10/001
Title of the study	A bioequivalence study comparing Fixed Dose Combination (FDC) of Rifampin and Isoniazid Tablets (containing Rifampin 150 mg and Isoniazid 75 mg) of Svizera Labs Mumbai, India with Rifinah [®] 150/300 mg (Isoniazid and Rifampicin) Tablets (containing Isoniazid 150 mg and Rifampin 300 mg) manufactured by Gruppo Lepetit SpA, Italy; marketed by Sanofi-Aventis, UK, in 28 healthy adult human male subjects under fasting condition.
Clinical part of the study: Name and address	Bombay Bioresearch Centre (BBRC) Plot N° 35, Deonar Ancillary Industrial Plots, Govandi, Mumbai - 400 043, India
Bio-analytical laboratory: Name and address	Bombay Bioresearch Centre (BBRC) Plot N° 35, Deonar Ancillary Industrial Plots, Govandi, Mumbai - 400 043, India
Date of inspection	11 - 15 October 2010

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.

General information about the site

BBRC started their clinical and bioanalytical operations for bioavailability / bioequivalence trials in November 2005. The CRO is located in a building built for purpose. There were 59 persons employed by BBRC at the time of the inspection according to the presentation made during the opening meeting, 49 according to the CRO master file provided to the inspectors during the inspection. This last figure included 17 persons in the clinical pharmacology unit, 14 in the bioanalytical laboratory, 4 in the data processing cell, 4 in quality assurance and 3 in "operational quality assurance". BBRC had completed 70 pivotal bioequivalence trials for various regulatory markets and 50 pilot studies according to the presentation, but a total of 138 trials according to the CRO master file.

The Clinical Pharmacology Unit was located on the ground floor of the building and the bioanalytical laboratory as well as quality assurance, documentation, data processing cell and the pharmacy were on the 1st floor. A 2nd floor was available for cafeteria and dining areas.

History of WHO and/or regulatory agency inspections

This CRO was previously inspected in January and April 2008 and in June-July 2009 by teams of inspectors from WHO. This was the fourth 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.

The site was previously authorised 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).

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). The effective implementation of some of the actions announced by BBRC in their Corrective action and Preventive action plan (CAPA) in response to the previous WHO inspection report was also checked during the visit of the facilities and during the inspection of the trial.

Focus of the inspection

On the first day of the inspection the CRO made a brief presentation. The facilities were then visited and explanations on some organization details were obtained.

The remaining investigational products from the study were retrieved from the humidity chamber in the pharmacy and their accountability and batch numbers were checked.

The archives were visited and the documentation from the clinical part of the trial was withdrawn from the archives and brought to the meeting room.

The inspectors went to the data processing cell to view on screen the Microsoft Excel spreadsheet which was used to calculate and report pharmacokinetic parameters from the data provided by the bioanalytical department.

On the second day of the inspection the inspectors reviewed the clinical trial master file. They returned to the archives to retrieve an additional binder which they had not been provided with initially. The organization of the archives was again discussed.

The inspectors reviewed the documents relating to the submission to, and approval by, the Ethics Committee of the protocol and subject information and consent forms, and discussed the insurance coverage of the subjects.

The inspectors checked the documentation relating to the receipt, storage, accountability, packaging and administration of the investigational products to the subjects. The consistency of these documents with information reported in the trial report (e.g. batch numbers) and with the randomization list was checked.

The inspectors checked the screening and study-specific informed consent forms signed by the subjects, for all subjects enrolled in the trial. They compared the signatures of the subjects on both forms to those on the "subject data slip" of period 1 and on the "custody of subject belongings and check in check out" forms. No abnormality was found.

The contents of the discharge cards signed by the subjects were checked. They contained no statement waiving subjects rights, in contrast with trials inspected during the previous inspection. The CAPA was correctly implemented for this aspect.

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The inspectors reviewed all documents available for a number of subjects:

- screening and trial case report forms
- pathology laboratory reports
- ECG's
- photocopy of the document provided by the subject to prove his identity and his date of birth.

The inspectors checked that the ECG's of these subjects were identical to those submitted to the WHO as part of the trial report. All subject ECG's had been checked before the inspection for abnormalities similar to those found during the previous inspection, where the authenticity of ECG's had been questioned. No abnormality was found.

The inspectors also checked for some subjects that blood sampling time deviations of more than 2 minutes had been reported in the trial report.

The inspectors checked the temperature records of -70°C freezer, where the plasma samples had been stored at the clinic during Period 1 and during Period 2, before being transferred to the bioanalytical laboratory. The temperature was recorded manually twice a day on working days and automatically every hour every day by data loggers.

On the third day of the inspection the inspectors reviewed the documentation relating to the validation of the bioanalytical method used for study sample analysis. Paper documents had been pulled from the archives and brought to the meeting room; the electronic version of the chromatograms was checked on screen in the laboratory. The following documents were reviewed:

- the laboratory notebook used to document daily activities. Extraction checklists were also briefly reviewed. The nominal concentration of the quality control samples used to study freeze/thaw cycles stability and long-term stability of the analytes in plasma was recalculated for isoniazid and rifampicin;
- the documentation on the origin of the blank plasma used to prepare calibration and quality control samples;
- the electronic version of the chromatograms of several analytical runs. The inspectors checked chromatogram integrations, re-integrations if any (none was found), the contents of the audit trail, variations in the internal standard response, and any time gap in the injection sequence. Concentrations or, when applicable, peak areas reported in the validation report were checked against the electronic raw data for isoniazid and rifampicin.

A number of runs were reviewed and the inspectors recalculated the nominal concentration of the calibration and control samples and checked that the correct nominal concentrations had been entered into LCQuan for the calibration samples. The inspectors recalculated the concentration of the calibration samples and of all samples analysed for precision and accuracy, using the peak areas and the calibration curve parameters. The

data of other samples analysed in that run were not checked against the report, but the chromatograms were reviewed.

On the fourth day of the inspection the inspectors continued their review of chromatograms of the method validation. Then a number of runs were reviewed, with the same systematic checks as on the previous day.

The inspectors reviewed the documentation relating to the preparation of stock and working solutions and of the calibration and quality control samples to be used for the analysis of study samples. The inspectors recalculated the nominal concentration of these samples.

The inspectors reviewed the laboratory notebook and extraction checklist forms used to document the preparation and analysis of study samples. The inspectors also briefly reviewed the freezer logbook in which the retrieval and re-storage of the plasma samples were documented. The inspectors noted that each run included the samples of two subjects for both trial periods. Each analytical run was therefore comprised of two batches of samples processed separately.

The inspectors reviewed the electronic version of the chromatograms of two subjects. The inspectors checked chromatogram integrations, re-integrations if any (none was found), the contents of the audit trail, variations in the internal standard response, any time gap in the injection sequence, and the correct entry into LCQuan of the nominal concentration of the calibration samples. Concentrations reported in the analytical report were checked against the electronic raw data for isoniazid and rifampicin. The inspectors recalculated the concentration of all calibration and quality control samples for these two analytes, from the peak areas and calibration curve parameters. The inspectors also recalculated the concentration of all samples of one subject for isoniazid and of the C max samples of both subjects for rifampicin.

The inspectors then checked the concentration reported in the analytical report for the quality control samples analysed with the samples of a number of subjects against the electronic version of the chromatograms. The inspectors did not review chromatogram integrations but checked that no re-integration had been made. The inspectors checked the acceptance criteria for these analytical runs and each extraction batch. This review was performed for isoniazid and rifampicin.

On the last day of the inspection the inspectors finalized the check of the concentrations of QC samples reported in the analytical report for a number of subjects and of the acceptance criteria of analytical runs and of each batch of samples. The inspectors reviewed the integration of the chromatograms of the calibration and QC samples in these runs.

The inspectors reviewed the electronic version of the chromatograms of two analytical runs of four subjects. The inspectors checked chromatogram integrations, re-integrations if any (none was found), the contents of the audit trail, variations in the internal standard

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response, any time gap in the injection sequence, and the correct entry into LCQuan of the nominal concentration of the calibration samples. Concentrations reported in the analytical report were checked against the electronic raw data for isoniazid and rifampicin. The inspectors recalculated the concentration of 4 sets of quality control samples for these two analytes in each of these two runs, from the peak areas and calibration curve parameters. They also recalculated the concentration of the C max samples of these 4 subjects for both analytes.

The inspectors reviewed the documentation relating to the checks of pipettes and reviewed the results of the daily checks of balance, on the days when the balance was used to weigh reference substances for the method validation and the study phase, and the report of the external check of the balance. This external check was done with weights traceable to national standards.

The inspectors reviewed the temperature records of freezers used to store study samples and QC samples for the determination of the long-term stability of the analytes in matrix. The temperature was recorded every hour by data loggers.

A summary of the inspection findings was presented to BBRC at the end of each day and as part of the inspection closing meeting.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, considering the findings of the inspection, including the observations listed in the Inspection Report, the data of study BBRC/EX/10/001 (TB189) were considered to be of an acceptable level of quality, and the study thus performed at an acceptable level of compliance with GCP and GLP as appropriate.

Part 4: Reference documents

1. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. *WHO Expert Committee on the Use of Essential Drugs. Sixth Report.* Geneva, World Health Organization, 1995 (WHO Technical Report Series, No. 850), Annex 3 http://whqlibdoc.who.int/trs/WHO_TRS_850.pdf
2. OECD Principles of Good Laboratory Practice (GLP). [C(97)186/Final], 1997 http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1,00.html
3. Additional guidance for organizations performing in vivo bioequivalence studies. WHO Technical Report Series, No. 937, 2006, Annex 9 <http://www.who.int/prequal>