

Prequalification of Medicines Programme
WHO PUBLIC INSPECTION REPORT
Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	TB180, TB181, TB182
Study number	See below
Title of the study	<p>Study No. : BEQ-050-RIP(F)-2006</p> <p>Study Title:</p> <p>An open label, randomized, two-treatment, two sequence, two period, two way crossover, bioequivalence study of ten dispersible tablets of fixed dose combination, each containing rifampicin 60 mg, isoniazid 30 mg and pyrazinamide 150 mg manufactured by Macleods Pharmaceuticals Ltd., India comparing with separate formulation of 4 capsules of Rimactane[®] 150 (each containing rifampicin 150 mg) of Novartis South Africa Ltd., 3 tablets of Isozid[®] 100 mg (each containing isoniazid 100 mg) of Fatol, Arzneimittel GmbH, Schiffweiler, Germany, and 3 tablets of Sandoz Pyrazinamide 500 (each containing pyrazinamide 500 mg) of Sandoz (Pty) Ltd., a Novartis company, South Africa in healthy, adult, male, human subjects under fasting conditions.</p> <p>Study No. : BEQ-049-RI (F)-2006</p> <p>Study Title:</p> <p>An open label, randomized, two-treatment, two sequence, two period, two way crossover, bioequivalence</p>

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	<p>study of ten dispersible tablets of fixed dose combination, each containing rifampicin 60 mg and isoniazid 30 mg manufactured by Macleods Pharmaceuticals Ltd., India comparing with separate formulation of 4 capsules of Rimactane[®] 150 (each containing rifampicin 150 mg) of Novartis South Africa (Pty) Ltd. and 3 tablets of Isozid[®] 100 mg (each containing isoniazid 100 mg) of Fatol, Arzneimittel GmbH, Schiffweiler, Germany, in healthy, adult, male, human subjects under fasting conditions.</p> <p>Study No. : BEQ-019-RI (F)-2005</p> <p>Study Title:</p> <p>An open label, randomized, two-treatment, two sequence, two period, two way crossover, bioequivalence study of ten dispersible tablets of fixed dose combination, each containing rifampicin 60 mg and isoniazid 60 mg manufactured by Macleods Pharmaceuticals Ltd., India comparing with separate formulation of 4 capsules of Rimactane[®] 150 (each containing rifampicin 150 mg) of Novartis South Africa (Pty) Ltd. and 6 tablets of Isozid[®] 100 mg (each containing isoniazid 100 mg) of Fatol, Arzneimittel GmbH, Schiffweiler, Germany, in healthy, adult, male, human subjects under fasting conditions.</p>
<p>Clinical Part of the study: Name and address of the organization</p>	<p>MacLeods Pharmaceuticals Limited G-2, Mahakali Caves Road, Shanti Nagar, Andheri - (East), Mumbai – 400 093 Tel.: 91-22-28306435 / 28314611 Fax: 91-22-28304641</p>

Bio-analytical laboratory: Name and address	MacLeods Parmaceuticals Limited G-2, Mahakali Caves Road, Shanti Nagar, Andheri - (East), Mumbai – 400 093 Tel.: 91-22-28306435 / 28314611 Fax: 91-22-28304641
Name and address of the Sponsor	MacLeods Parmaceuticals Limited G-2, Mahakali Caves Road, Shanti Nagar, Andheri - (East), Mumbai – 400 093 Tel.: 91-22-28306435 / 28314611 Fax: 91-22-28304641
Date of inspection	25 and 26 February 2009

Part 2: Summary

General information about the site(s)

After arrival at the site, the company representatives introduced themselves and made a presentation about the company. MacLeods was established in 1986 and employed 4500 people. The main focus of products manufactured were anti-TB, anti-malaria, antiretrovirals, antibacterial products and others. Manufacturing sites were located in mainly in Daman and Baddi (finished products). The company also manufactured APIs.

The inspectors were informed that the CPU was expanded from 28 beds to 40 beds. There was about 104 staff members employed at the time of the inspection. About 40 studies (including pilot studies) were conducted annually.

Personnel worked in two to three shifts per day.

History of WHO and/or regulatory agency inspections

The bioavailability centre was located in Mumbai and started operations in April 2005. It was previously inspected by WHO inspection teams in April 2006, May 2006, January 2007, April 2007 and September 2007. The site was also inspected by USA FDA in March 2008.

Focus of the inspection

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

Inspected Areas

On the first day of the inspection, focus was placed on clinical parts of the studies, and on the second day focus was placed on the bio-analytical part of the studies. Source data were inspected and verified against the submitted data in product dossiers. Compliance with GCP was assessed.

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Documents inspected included source data (which included comparison to dossier data) for e.g.:

- Drug product data and information including receipt and correspondence for test and reference products
- Labelling of product and vials
- Record of transfer of samples to the -20C deep freezer, and from -20 to -50 degrees C deep freezer
- Curriculum vitae of various persons
- Monitor manual
- Monitor report /checklist
- Initiation of clinical operations

- Protocol training attendance
- Delegation of duties
- Emergency medicines checklist
- Obtaining study specific ICF
- Master list of volunteers
- Subject check in record
- Drug dispensing forms
- Randomization schedule
- Record of standardized meals
- Custodian reports
- Cannulation record
- Check out record
- Deviation forms
- Drug accountability forms
- Screening consent
- Study specific ICF
- Proof of payment (compensation)
- Training records for selected individuals
- Dosing forms, labels and related documents
- Case report forms (CRFs) and laboratory reports for subjects 10, 15, 29 and 31
- Training record for the monitor
- QA audit report for the clinical part of the study

After reviewing the documents listed above, the inspectors walked through the CPU and asked questions related to the activities. A few documents were checked in the CPU e.g. log books for the use of the ECG machines, calibration of ECG (machine no 03).

Some documents were verified for study No: BEQ-019-RI (F)-2005.

On the second day, bio analysis was inspected. This included the review of documentation and raw/source data covering

- Method validation (precision, accuracy, ruggedness)
- Cross validation (anticoagulant effect CPDA and Heparin)
- Stability (including freeze thaw, long term)
- SOP for re-analysis
- Tabulated information for re-analysis
- Subject sample analysis - subject 9, 15, 19, 22 and 26
- Form 11 for subject 9 (re-analysis)
- Source data and chromatograms including manual back calculation for S9 and S16 repeat analysis done
- Deep freezer log for placement and withdrawal of samples to verify number of samples for specific runs
- Subject sample analysis (15 and 16 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)

- Subject sample analysis (19 and 20 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)
- Subject sample analysis (21 and 22 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)
- Subject sample analysis (26 and 20 in one run) - raw data, chromatograms, sample sequence, QCs and CC and back calculation - PI and PII (selected time points)
- QA report for bio-analysis
- SOP for failure investigation
- Calibration of micro pipettes
- Calibration of the analytical balance
- Centrifuge including calibration and PQ
- HPLC records and calibration for column oven temperature
- A visit to the deep freezers and refrigerator
- Supplier manual (centrifuge)

Besides the observations listed in the full inspection report, the following areas were considered to be compliant with GCP:

1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL
2. THE PROTOCOL
3. PROTECTION OF TRIAL SUBJECTS
4. RESPONSIBILITIES OF THE INVESTIGATOR
5. RESPONSIBILITIES OF THE SPONSOR
6. RESPONSIBILITIES OF THE MONITOR
7. MONITORING OF SAFETY
8. RECORD-KEEPING AND HANDLING OF DATA
9. STATISTICS AND CALCULATIONS
10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS
11. ROLE OF THE DRUG REGULATORY AUTHORITY
12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

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:

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containing pyrazinamide 500 mg) of Sandoz (Pty) Ltd., a Novartis company, South Africa in healthy, adult, male, human subjects under fasting conditions.

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were considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at MacLeods Pharmaceuticals Limited, G-2, Mahakali Caves Road, Shanti Nagar, Andheri - (East), Mumbai – 400 093.

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
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