



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	HA 511 and RH030
Study number	09-04-302 (HA511) and 09-06-319 (RH030)
Title of the study	<u>HA511:</u> Bioequivalence study comparing the Nevirapine 100 mg tablet for oral suspension of Cipla Ltd., India with Viramune® oral suspension (containing Nevirapine 50 mg/5 ml as Nevirapine hemihydrate) of Boehringer Ingelheim, Inc., USA both administered as Nevirapine 200 mg in healthy adult human subjects under fasting conditions. <u>RH030:</u> Bioequivalence study comparing Levonorgestrel 150 mcg and Ethinylestradiol 30 mcg combination tablet of Cipla Ltd., India with Microgynon® tablet (containing Levonorgestrel 150 mcg and Ethinylestradiol 30 mcg) of Schering Healthcare Ltd., UK in healthy postmenopausal female human subjects under fasting conditions.
Clinical Part of the study: Name and address of the organization	Sitec Labs Pvt Ltd 1 st Floor, Jashree Plaza, Near Dreams Mall, L.B.S. Marg, Bhandup (West), Mumbai, 400 078, INDIA
Bio-analytical laboratory: Name and address	Sitec Labs Pvt Ltd Pee-Dee Info Tech. Plot No Gen 40, TTC, MIDC, Behind Millennium Business Park, Near Nelco, Mahape, Navi Mumbai 400 701, INDIA
Date of inspection	14 to 15 February 2012 (Bio-clinical) 16 to 17 February 2012 (Bio-analytical)

Part 2: Summary

General information about the site(s)

Sitec Labs started its clinical and bio-analytical operations for bioavailability / bioequivalence studies in December 2004. In addition to BA/BE studies, Sitec also performs testing of pharmaceutical products. There are currently 40 staff employed by Sitec Labs in Clinical and 52 staff in Bio-analytical excluding QA staff.

The clinical and bio-analytical studies for HA511 and RH030 were conducted between August 2009 and February 2010 at Jayshree Plaza, 1st Floor b L.B.S. Marg, Opp. R.R. Paints Bhandup (West), Mumbai 400078, where the first two days of the present inspection was conducted (clinical part). As the bio-analytical section was moved to a new location in September 2010, the last two days of the present inspection was conducted (Bio-analytical) at Sitec Labs Pvt Ltd Pee-Dee Info Tech. Plot No Gen 40, TTC, MIDC, Behind Millennium Business Park, Near Nelco, Mahape, Navi Mumbai 400 701, India.

History of WHO and/or regulatory agency inspections

Sitec Labs Pvt Ltd was previously inspected by WHO in, 2006, 2008 and 2009 and this was the fourth WHO inspection on Sitec Labs Pvt Ltd. In addition, Bio Studies had been successfully inspected and approved by the following authorities:

- EMEA
- MCC
- US-FDA

In addition, laboratory was certified with ISO 9001:2008 and ISO 17025:2005 standard by Q.A. International certification UK.

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product Nevirapine 100 mg tablet for oral suspension (HA511) and Levonorgestrel 150 mcg and Ethinylestradiol 30 mcg combination tablet (RH030). 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

Day 1 (Clinical section)

- Registration area
- Screening and enrolment of subjects
- There were 3 ECGs available at site. It was claimed that only one ECG was in use. The pre-numbered thermal papers were used to printout ECG.
- Physical examination room

- Blood collection room
- Change room/toilet facilities
- CPU I and II
- Phlebotomy room
- Ambulatory care medicine inventory and expiry dates
- Centrifuge room
- Recreation room
- ICU (defibrillators, suction machine, oxygen cylinders, etc.)
- Pharmacy: verification of reference and test products
- The sample processing and storage areas were visited.
- Master Service agreement between Sitec Labs and Cipla Limited (sponsor).
- Insurance (Bajaj Allianz) was purchased for these studies for a period 25th Jan 2009 to 24th Jan 2010.
- Calculation of compensation of the subject for study was reviewed.
- Volunteer information document, volunteer consent and declaration form
- Meeting attendance and signatures
- Authorised signatures/role and responsibilities form
- Monitoring visit reports
- Training record of Rajam.
- Attendance sheet of protocol meeting and CV of PI
- Volunteer consent forms for screening (in Hindi) reviewed.
- SAS output for randomization list with signature of statistician
- Case report form and dosing record of subject numbers 1 and 5 reviewed.
- SOP on dispensing of investigational products
- Calibration report of analytical balance used in the study
- Change room (toilet and shower)

Day 2 (Clinical section)

- Shipping letter receipt of reference product
- Dispensing form
- Reconciliation form
- Temperature and humidity record of walk in humidity chamber
- Labels for syringes and polybags
- Deep freezer logbook
- Independent ethic committee minutes of meeting
- List of authorized signatures, roles and responsibilities form
- Volunteer consent form for screening in Marathi, Hindi and English for all subjects

Day 3 (Bio-analytical)

- Sample receipt record
- Freezer logbook
- Sample signature list
- Minutes of meeting (pre-study)

- Sample storage area
- Sample processing lab
- Balance room and reference/internal standards
- Instrument room
- CV of Principal Investigator
- Monitoring report/audit certification
- Training records on method validation
- List of personnel and specimen signatures
- SOP on preparation of method of analysis
- Validation of method (partial)
- Certificate of analysis of working standard
- Plasma issue report
- Verification of calculations of calibration curve and QC (LQC and LLOQ)
- Precision and accuracy of Nevirapine
- Freeze thaw study
- Long term stability
- Preparation of stock solution and verification of stock A1, A2 and then CCs and QCs
- Preparation of standard stock solution and preparation of stock levels for CCs and QCs
- Verification of calculations for CCs and QCs and preparation of internal standard
- Calculation verification for subject (LQC, MQC)
- Calculation verification for subject (HQC and MQC)

Day 4 (Bio-analytical section)

- Log for transfer of plasma samples to analytical laboratory
- Stock solution for validation and review of chromatograms for subjects for Period I and Period II
- SOP on subject samples analysis
- SOP on evaluation of chromatographic data
- Back calculation of CCs from stock solution
- Stock solution stability
- Precision and accuracy
- Subject analysis for subject 1 to 6
- Authorization of repeat analysis
- Subject analysis for subject 7, 8 and 9
- Verification of QCs which were borderline and repeated ones
- Verification of subject analysis using different LCMS/MS system
- List of equipment transferred from old Sitec BAL lab
- Pictures from previous laboratory

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

Most of the necessary prerequisites were considered to be fulfilled in general.

2.2. THE PROTOCOL

In general, protocol was found acceptable. The protocol was approved by the ethic committee.

2.3. PROTECTION OF TRIAL SUBJECTS

This area was found to be unacceptable to WHO GCP requirement. However, as a corrective action and preventive action, Sitec has confirmed that illiterate subjects will not be recruited for any of the future studies. In addition, due consideration will be given to confirm independence of ethic committee.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

Responsibilities of the investigator covered all of the elements prescribed by the WHO GCPs.

2.5. RESPONSIBILITIES OF THE SPONSOR

No issues of concern were noted.

2.6. RESPONSIBILITIES OF THE MONITOR

Monitoring was found inadequate as there were no monitoring reports available for before and after the study. However, appropriate corrective and preventive actions have been proposed.

2.7. MONITORING OF SAFETY

Both the CRO and the applicant were responsible for the reporting of adverse events to the regulatory authorities.

2.8. RECORD-KEEPING AND HANDLING OF DATA

The necessary records were available. Appropriate corrective and preventive actions have been proposed.

2.9. STATISTICS AND CALCULATIONS

Randomization was performed using SAS and subjects were randomized through order of arrival. Statistical analysis was not covered during the inspection.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

Supply and storage were documented in detail. Reconciliation details of the test and reference product were available and found accurate.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

This aspect was not covered during this inspection.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

An audit report, detailing the control of the activities related to the trial, was available. However, it has been noted that some of the raw data entries were corrected in a way which obscures the original information.

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 **HA511** was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at *Sitec Labs Pvt. Ltd at Bhandup (West) for Clinical and Mahape, Navi Mumbai for Bio-analytical*.

For **RH030**: Although, certain aspects of the study were not performed in accordance with WHO GCP standard (in particular use of illiterate subjects), it was observed that this alone didn't justify repetition of the study and furthermore, the actions taken or proposed to be taken in relation to this observation in future studies were found to be satisfactory. In view of the above, the study, reference **RH030**, is considered acceptable to support the product.

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.