



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	(a) RH038 Levonorgestrel 0.15mg and Ethinylestradiol 0.03mg tablets (b) HA570 Nevirapine tablets USP 200mg
Study number	1. Study # ARL/08/008 2. Study # ARL/10/530
Title of the study	1. “A Open Label, Randomized, Two- Sequence, Two-Treatment Two-Period, Crossover, Single Dose, Bioequivalence Study of Fixed Dose Combination of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg Tablets of Famy Care Ltdwith Microgynon [®] 30 (Fixed Dose Combination of Levonorgestrel 0.15 mg and Ethinylestradiol 0.03 mg) Tablets of Schering Pharma, in Normal, Healthy, Adult, Female Human Subjects Under Fasting Condition.” 2. A Randomized, Open Label, Balanced, Two-Treatment, Single-Period, Single Dose, Parallel, Bioequivalence Study of Nevirapine Tablets USP 200 mg of Micro Labs Ltd., INDIA with Viramune [®] (nevirapine) 200 mg Tablets of BoehringerIngelheim Pharmaceuticals, Inc., USA, in Normal, Healthy, Adult, Human Subjects Under Fasting Condition.
Clinical Part of the study: Name and address of the organization	Accutest Research Lab (I) Pvt. Ltd. 4 th Floor, The Grand Monarch, Near Seema Hall, Anand Nagar Road, Satelite, Ahmedabad-380015, INDIA
Bio-analytical laboratory: Name and address	Accutest Research Lab (I) Pvt. Ltd Opp. The Grand Bhagwati Hotel, Sarkhej - Gandhinagar Highway, Bodakdev, Ahmedabad - 380059, India
Date of inspection	10 - 13 December 2013

Part 2: Summary

The purpose of the inspection was to inspect the clinical and the bioanalytical part of the bioequivalence studies performed at Accutest Research Laboratories (I) Pvt Ltd (hereafter ARL) Ahmedabad (Unit I and II) and to evaluate whether the studies were conducted in compliance with the protocol, Good Clinical Practices (GCP) and Good Laboratory Practices (GLP) where applicable.

General information about the site(s)

ARL was founded in 1998, and its headquarter is located in Navi Mumbai. It is a diversified Contract Research organization (CRO) which provides services in the field of Bioavailability / Bioequivalence, Formulation Development, Clinical Trials & Data Management and Analytical services for Biologics and Biosimilars. ARL facilities are spreaded across sites in Mumbai, Ahmedabad, Vadodara and Mexico (only bioanalytical services).

ARL Ahmedabad (India) was inspected on the above-mentioned dates. ARL Ahmedabad had two units:

- a) Unit I, located on 4th floor; The Grand Monarch, Near Seema Hall; Anand Nagar Road, Satellite, Ahmedabad - 380015, India
- b) Unit II, located opposite The Grand Bhagwati Hotel, Sarkhej - Gandhinagar Highway, Bodakdev, Ahmedabad - 380054, India

ARL Ahmedabad had total of 176 beds across over Unit I and II. The bioanalytical facility is based at Unit II which housed 14 LC-MS/MS systems.

History of WHO and/or regulatory agency inspections

The CRO had undergone several inspections from various regulatory authorities such as:

- WHO
- MCC
- USFDA
- UKMHRA
- ANVISA
- ISP Chile
- Turkey and DCGI, India

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product **RH038** (Levonorgestrel 0.15mg and Ethinylestradiol 0.03mg tablet). In addition, some bioanalytical aspect of **HA570** (Nevirapine 200mg tablets) were briefly inspected. The inspection covered most of the sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Inspected Areas

A. CLINICAL PART

1. Overview of clinical part presentation
2. Physical tour of clinical area including:
 - Registration (this will include an examination of the databases in use and means of retaining information on subjects)
 - Screening (instruments used)
 - Subject change rooms
 - CPU
 - ICU
 - Pathology laboratory
 - Pharmacy
3. Documentation review
 - Contract between Sponsor and investigator
 - Review of Sponsor responsibilities
 - Review of CRO responsibilities
 - Principle Investigator and staff involved in the study
 - Review of Ethics Committee composition, responsibilities, SOPs, detailed minutes of meetings discussing the study under review
 - Review of Protocol, volunteers, ICF, Screening and CRFs
 - Verification of Source data
 - QA Audit reports
 - Monitor reports
 - Randomization
4. Pharmacy and investigational products
 - Site inspection. CPU
 - Dosing
 - Storage
 - Reconciliation of IPs
 - Line clearance procedures and documentation.
5. Sample collection, preparation and storage
 - Visit of applicable areas and of refrigerators, deep freezers and ultra-deep freezers in use.
 - Qualification and performance verification of equipment.
6. Archives (paper and electronic)
 - Access control
 - Document traceability
 - Protection of documentation and

B. BIOANALYTICAL PART

1. Overview and brief visit of facilities and equipment
2. Management of computerized systems and protection of data (verification of documentation vs. practice)
3. Review of source data in electronic and hard copy (Sample analysis for Period I and Period II)
 - Back calculations
 - Acceptability of runs
 - Review of source data (Preparation of matrix, stock, QCs and stability (weighing, calculations, and chromatograms, method development and validation)
4. Reanalyses, repeat analyses, ISR
5. Bio-analytical Method development
6. Bio-analytical Method validation data
 - SOP
 - Protocol and report
 - Precision, accuracy etc.
7. Plasma selection and pooling
8. Stock solution preparation
 - QCs
9. Stability data (stock solution and samples)
 - Short term
 - Long term
 - Freeze thaw
 - In injector/Autosampler
10. Laboratory inspection
 - Instruments and equipment
 - Pipettes
 - Sample management
 - Deep freezers
 - Reference standards
 - Fridges

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

This part of the bioequivalence trials was found to be satisfactory overall for the study examined and for the facilities.

2.2. THE PROTOCOL

For the studies that were inspected, protocols were considered to be acceptable overall.

2.3. PROTECTION OF TRIAL SUBJECTS

The declaration of Helsinki as per the Good Clinical Practices (GCP) principles was displayed. The observation raised from this section has been addressed adequately, and the same will be verified during future inspections.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

In general, this section of GCP was found to be satisfactory. The observation raised from this section has been addressed adequately, and the same will be verified during future inspections.

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

There was one monitoring visit carried out of the study, this does not meet the minimum expectation of performing three monitoring visits. The matter was eventually addressed satisfactorily by the sponsor, and the same will be verified during future inspections.

2.7. MONITORING OF SAFETY

Subjects were monitored for safety during the study and until the completion of the study. Safety assessments were done based on clinical observations, laboratory data at the beginning and at the end of the study and evaluation of the adverse events (AEs) observed during the course of the study.

The observation raised from this section has been addressed adequately, and the same will be verified during future inspections.

2.8. RECORD-KEEPING AND HANDLING OF DATA

Handling of data was considered acceptable. Study records were stored in the CRO archive which was found to be adequately controlled.

2.9. STATISTICS AND CALCULATIONS

Methods of communicating the information between bioanalytical and the Pharmacokinetics (PK) department were verified and found to be acceptable. It was noted that the quality control and quality assurance after due diligence forwarded the data to PK department via email. Upon transferring the received data into the format for Winnolin, the PK department forwarded the data for final verification to QC

before being used to perform the PK study. The randomization schedule was verified for some of the subjects and was adhered to.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

The pharmacy had an adequate facility for handling, storage and dispensing of the investigational products. The quantities of test and reference product in question were verified and found acceptable. Dispensing was done in accordance with an SOP.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

The Central Drugs standards control Organization (CDSCO) had licensed the CRO for carrying out the clinical studies.

2.12. 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. In general, this area was considered to be 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, as well as the corrective actions taken and planned, the study *RH038 and HA570* were considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at *Accutest Research Lab (I) Pvt Ltd, Ahmedabad, India*.

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.