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WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	RH037
Study number	RH037 (Desogestrel and Ethinylestradiol Tablets 150mcg/30mcg)
Title of the study	An open label, balanced, randomized, two-period, two-treatment, two-sequence, crossover, single oral dose, comparative bioequivalence study of Desogestrel + Ethinylestradiol 0.15mg/0.03mg Tablets (Test) of Famy Care Limited, India and 'MARVELON' (Desogestrel + Ethinylestradiol, 0.15mg/0.03mg) Tablets of N. V. Organon Oss in healthy adult female subjects under fasting condition.
Clinical Part of the study: Name and address of the organization	Cliantha Research Ltd. 1st floor, Silver Arcade, Near Ashwamegh III, Samrajya, Mujmahuda Road, Akota, Vadodara-390020, Gujarat, INDIA
Bio-analytical laboratory: Name and address	Cliantha Research Limited, BA Research House, Opposite Pushparaj Towers, Near Judges Bungalows, Bodakdev, Ahmedabad, 380054, Gujarat, INDIA
Pharmacokinetic part of the study Name and address	Cliantha Research Limited Sigma-1 Corporate, B/H. Rajpath Club, Opposite Mann Party Plot, Off. S.G Highway, Bodakdev, Ahmedabad.-380 054, Gujarat, INDIA
Date of inspection	19 - 22 March 2013

Part 2: Summary

General information about the site(s)

Cliantha Research Limited is a global contract research organization, specialized in conducting Bioavailability, Bioequivalence studies, dermatology studies, Clinical Trials (Phase I to IV), Clinical Data Management and Biometrics. The company was established as BA Research India Limited in 2004 and has been renamed in 2011 as Cliantha Research limited. Cliantha Research Limited has facilities across three different sites, out of which two sites are located at Ahmedabad (Cliantha Research House and Sigma Corporate) and third site is located at Vadodara.

Vadodara facility: Vadodara facility has a 34 000 square feet area. The facility comprises screening area, 4 clinical units and quality assurance unit. The entire first floor has total 200 beds, divided into 4 clinics. Clinic-I & IV has 60 beds with ICU beds in each clinic. Clinic-II and Clinic-III has 40 beds with ICU bed in each clinic. Each site has separate pharmacy facility. Archiving facility and clinical laboratory is situated at Vadodara and Sigma locations. Each clinical unit is in controlled access with its own dining area, bed area, recreation area, sample collection, sample separation and storage area.

History of WHO and/or regulatory agency inspections

Cliantha Research Limited had been inspected by following regulatory agencies.

a. AFSSAPS (ANSM), 6-11 November 2006 – Cliantha House
b. USFDA, 14-17 May 2007 – Cliantha House
c. USFDA, 20-21 September 2007 – Cliantha House
d. USFDA, 15-19 September 2008 – Cliantha Vadodara
e. MCC, 12-13 January 2009 – Cliantha House
f. USFDA, 17-23 June 2010 – Cliantha house
g. WHO, 18-20 October 2010 – Cliantha House
h. USFDA, 18-22 October 2010- Cliantha Sigma
i. USFDA, 25-27 October 2010 –Cliantha House
j. AUSTRIAN (AGES), 09-10 February 2011- Cliantha Vadodara
k. SPAIN (AEMPS), 11-15 April 2011 – Cliantha House & Cliantha Vadodara
l. USFDA , 03-07 October 11 – Cliantha Vadodara
m. WHO, 19-22 June 12 – Cliantha House & Cliantha Sigma
n. MHRA, 25-28 February 2013, 1 March 2013 – Cliantha House & Cliantha Sigma
o. The facilities are approved by Drug Controller General of India (DCGI).

This was the first WHO inspection at their Vadodara clinical facility.

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the Desogestrel and Ethinylestradiol Tablets 150mcg/30mcg tablet (RH037). 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

A. 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

B. 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
    - Statistical analysis

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 study that was inspected, protocol was 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 in the presentation area both in vernacular Gujarati and English language. The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

In general, this section of GCP was found to be satisfactory. The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.5. RESPONSIBILITIES OF THE SPONSOR

The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.6. RESPONSIBILITIES OF THE MONITOR

The in-house quality control and quality assurance (QA) had monitored the study based on their in-house procedure and found acceptable in general. The organogram presented confirm the independence of QA.

The observations raised from this section had been adequately addressed, and the same shall be verified during the next inspection.

2.7. MONITORINGOFSAFETY

The subjects were assessed before the entry of subjects into study as per the selection and withdrawal criteria stated in the protocol. The vital signs and clinical examination were conducted as per the protocol. Also, the protocol required handling and reporting of adverse events and serious adverse events. In general, this area was found satisfactory.

2.8. RECORD-KEEPING AND HANDLING OF DATA

The source data were adequately documented for various activities performed during the conduct of the study. The procedure for the blood sampling time deviation was adhered to. The deviations were reported and also taken into account when statistical analysis was performed.

The archives and electronic records were found to be acceptable overall. The Vadodara facility was equipped with an adequate archive facility for both paper and backup disks.

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 (100% check) and quality assurance (20% check) 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. These data were not shared on the common drive to prevent potential misuse.
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.

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. An observer from the CDSCO was present and observed the WHO inspection.

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 *RH037* was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at Cliantha Research Limited conducted at Vadodara (clinical) and Ahmedabad (bio-analytical).

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.