



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	HA527, TB253, HA520 Other products considered (spot-checks only): HA540, HA551
Study number	HA527: Study #: 1017/10 TB253: Study #: 2005/10 HA520: Study #: 227_DIDAN_06 And: HA540: Study #: 1027/11 HA551: Study #: No. 2033/11
Title of the study	1. HA527: An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover bioequivalence study comparing fixed dose combination tablets of efavirenz 600 mg, emtricitabine 200 mg & tenofovir disoproxil fumarate 300 mg of Ranbaxy Laboratories Limited with the reference product, in healthy, adult, human subjects under fasting condition. 2. TB253: It was an open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study comparing Moxifloxacin hydrochloride 400 mg tablets of MSN Laboratories Limited with the reference product, in healthy, adult human subjects under fasting conditions 3. HA520: An open label, balanced, randomized, two-treatment, two-sequence, four-period, single-dose, crossover, fully replicated bioavailability study on didanosine formulations comparing didanosine 400 mg delayed release capsule of Ranbaxy Laboratories Limited with the reference product, in healthy, adult, male, human subjects under fasting condition.
Clinical Part of the study: Name and address of the organization	Clinical Pharmacology Unit Ranbaxy Laboratories Ltd., Hakeem Abdul Hameed Centenary Hospital, otherwise named as “Majeedia Hospital” (2nd Floor)

	Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062 AND Clinical Pharmacology & Pharmacokinetics Ranbaxy Laboratories Limited Plot No. GP-5, Sector 18, HSIDC Old Delhi –Gurgaon Road Gurgaon 122 015, Haryana India Note: Another site was used by Ranbaxy to perform the clinical portion of 2005/10, 227 DIN 06 and 2033/11. It was not part of the on-site inspection.
Bio-analytical laboratory: Name and address	Ranbaxy Laboratories Limited Clinical Pharmacology and Pharmacokinetics unit (CPP) Plot No. GP-5, Sector 18, HSIDC Old Delhi –Gurgaon Road Gurgaon 122 015, Haryana India
Date of inspection	2 to 6 September 2013

Part 2: Summary

General information about the site(s)

Ranbaxy Labs Pvt Ltd was performing comparative clinical bioequivalence studies on their own products at 2 clinical facilities near New Delhi, named Hakeem Abdul Hameed Centenary Hospital and Noida. Bioanalysis and clinical laboratory testing for screening and safety purposes were performed at the CPP unit in Gurgaon. Only the Hakeem Abdul Hameed Centenary Hospital, New Delhi and CPP unit in Gurgaon were the object of this inspection. The Noida CPU was not within the scope of this inspection.

The Majeedia Hospital facility had a capacity of 72 beds with live monitoring, phlebotomy, integrated dining and recreation areas. The bioanalytical facility in Gurgaon was equipped with 24 LC-MS/MS systems, of which 23 were operated using Analyst[®], and 1 using MassLynx[®]. Analyst[®] (version 1.4.1 for the HA527 and TB253 studies) was used to perform the bioanalytical portion of the studies under the scope of this inspection.

History of WHO and/or regulatory agency inspections

The last WHO inspection was performed in December 2011 and covered 2 WHO products (HA497 and HA509). This inspection was performed as a joint inspection with the MHRA and ANSM.

The clinical laboratory at Gurgaon was certified ISO 15189:2007 (“Medical laboratories Particular requirements for quality and competence”). The accreditation was given by the NABL (National Accreditation Board for Testing and Calibration Laboratories”. The laboratory was also certified by the College of American Pathologists.

Focus of the inspection

The inspection focused mostly on the bio-equivalence study conducted for HA527 (efavirenz 600 mg, emtricitabine 200 mg & tenofovir disoproxil fumarate 300 mg tablets), TB253 (Moxifloxacin 400 mg tablets) and spot-checks on HA520 (Didanosine 400 mg delayed-release capsules). Inspectors from MHRA and ANSM focussed on other studies/ product and inspected the studies and sites in accordance with their applicable guidelines. The WHO inspector performed this inspection covering all the sections of the WHO GCP and GLP texts, including the WHO guidance for organizations performing in vivo bioequivalence studies. Each inspector reconstructed the various studies under review by inspecting Case Report Forms, the respecting of the protocol’s inclusion/exclusion criteria, laboratory reports for screening and ambulatory tests, electro-cardiograms (ECGs) (ANSM), informed consent forms (for screening and the trial), proof of ID, allotment of subject ID numbers, subject payment records and signatures, allocation of responsibilities of trial personnel, segregation of samples and labelling for both studies.

Inspected Areas

Days 1 and 2 focussed mostly on the general organization of the Hakeem Abdul Hameed Centenary Hospital site as well as on the clinical portion of both studies, while days 3, 4 and 5 focussed mostly on the bioanalytical portion of each study. The remaining points and closing meeting were given on day 5. Further statistical examination of the subject concentration data was performed after the inspection.

2.1. PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

This area was found to be generally acceptable. The trials seen were adequately justified in the view of the fact that they were bioequivalence studies for well-known and currently marketed medicines.

2.2. THE PROTOCOL

This area was found to be generally acceptable although a minor deficiency was found with regards to the control of the different versions of the protocol that was sent to the independent ethics committee. That was corrected by the company for future studies.

2.3. PROTECTION OF TRIAL SUBJECTS

Protection of trial subjects was deemed to be acceptable overall although issues were found which were addressed in the company’s corrective and preventive actions for future studies.

2.4. RESPONSIBILITIES OF THE INVESTIGATOR

For Hakeem Abdul Hameed Centenary Hospital: The state and configuration of the areas used for subject registration, screening, check-in, clinical wards, beds, restrooms, and recreation were inspected on Day 1 and were acceptable overall.

Identification and tracking of subjects was performed using a combination of verification of names through the use of ID cards, photos and subject information was recorded and tracked using a biometric/fingerprint recognition system connected to database shared between Ranbaxy and collaborating CROs in New Delhi.

The areas for informed consent, screening, toilets, beds (which included recreational and dining areas), sample processing and temporary sample storage, phlebotomy stations and supply areas were also visited. X-rays were performed at the hospital, if judged necessary by the physician responsible for screening.

The company stated that their database included 5000 trial subjects, including 225 women volunteers.

For Gurgaon: The archives were inspected and were verified to have appropriate access control, protection from fire of the documents, as well as recordings of documents withdrawn and returned.

2.5. RESPONSIBILITIES OF THE SPONSOR

The investigator and sponsor were part of the same commercial entity in this case.

2.6. RESPONSIBILITIES OF THE MONITOR

Monitoring was performed by Ranbaxy since both the sponsor and investigator were both under the same commercial entity.

2.7. MONITORING OF SAFETY

This area was found acceptable overall.

2.8. RECORD-KEEPING AND HANDLING OF DATA

Archiving and handling of data was found to be acceptable overall although the practices and policies for back-ups and archiving of electronic data would have deserved a closer look.

2.9. STATISTICS AND CALCULATIONS

The statistical department was inspected and this area was found acceptable in general.

2.10. HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

The pharmacy of the Hakeem Abdul Hameed hospital clinical unit was visited by one of the teams on Day 2 and drug product accountability, line clearance procedures were verified.

Study drug certificates of analysis were reviewed for the reference products relevant to the studies under inspection. Original documents were not available, but certified copies were.

Accountability of reference and test product was verified for both studies and was found to be acceptable. Traceability was ensured through the keeping of both the remaining test and reference product, entry and withdrawal records for the stability chamber, as well as stock cards for each product.

2.11. ROLE OF THE DRUG REGULATORY AUTHORITY

This was not verified during the inspection.

2.12. QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

A system of quality assurance covering both clinical and bioanalytical aspects was generally in place. Quality control procedures were applied to each stage of data handling.

2.13. BIOANALYTICAL DATA

On day 3, ultra deep freezers and deep freezers in the bioanalytical area were examined. A centralized and online temperature monitoring system was under installation (target implementation date according to the Company presentation: 30 April 2014). The remaining samples for both studies were examined to verify the labelling and the absence of mix-ups. Temperature records were examined for the ultra-deep and deep freezers used for both studies, for samples, blank plasma and spiked plasma preparations, at different times during the inspection to confirm that they were stored within acceptable ranges.

A brief look at the HPLC-MS/MS, chromatographic column storage, reference standards, sample preparation equipment, was taken. Analytical balances and the presence of suitable calibration standards was also verified.

Further to these verifications, inspectors proceeded to a review of the bioanalytical data for their different studies simultaneously (on Day 3 for tenofovir (1017/10 study) and was continued on Days 4 and 5 for moxifloxacin and didanosine (fasted portion of the study).

Adequate records were generally maintained. Records generally allowed full traceability of the equipment used which was also, in turn, traceable to calibration records.

Integrations were consistent and performed according to company SOPs. Instrument, project and results table audit trails were used.

2.14. CLINICAL LABORATORY

The clinical laboratory was inspected on Day 5. Tests were run using modern and calibrated multi-purpose automated equipment. Sample results were directly linked to the subject's files using a barcoding system. This area was generally found 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, study # **1017/10 (HA527) was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at the Hakeem Abdul Hameed Centenary Hospital and CPP Gurgaon facilities.** Also, the bioanalytical portion of study # **2005/10 (TB253), was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at the CPP Gurgaon facilities**

Furthermore, according to the spot-checks that were made, **no GCP/GLP issues of significant concern were found** with regards to study # **227_DIDAN_06 (HA520)**, study # **1027/11 (HA540)**, study # **2033/11 (HA551)** and with regards to the clinical portion of study # **2005/10 (TB253).**

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.