

WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Contract Research Organization

Part 1: General information

WHO product numbers covered by the inspection	Didanosine 400mg capsule
Study number	BA08101071-01
Title of the study	An Open Label, Randomized, Two Period, Two Treatment, Two Sequence, Crossover, Balanced, Single Dose Comparative Evaluation Of Relative Bioavailability Of Didanosine Delayed Release Capsules 400 mg comparing with that of 'VIDEX [®] EC' Delayed Release Capsules 400 mg, made in Bristol-Myers Squibb Company, Princeton, NJ 08543, USA (containing Didanosine Delayed Release Capsules 400 mg) in Healthy Adult Human Subjects Under Fasting Conditions
Clinical part of the study: Name and address	BA Research India Ltd. BA Research House, Opp. Pushparaj Towers Nr. Judges Bungalows Bodakdev, Ahmedabad-380 054 India
Bio-analytical laboratory: Name and address	BA Research India Ltd. BA Research House, Opp. Pushparaj Towers Nr. Judges Bungalows Bodakdev, Ahmedabad-380 054 India
Date of inspection	18-20 October, 2010

Part 2: Summary

The purpose of the inspection was to inspect the bio-equivalence study performed at BA Research India (hereafter referred to as BA, to assess compliance with GCP, GMP and GLP (as appropriate) and to verify the related source data for the above mentioned study.

General information about the site

BA, located at BA Research House, Opp. Pushparaj Towers Nr. Judges Bungalows Bodakdev, Ahmedabad-380 054 India was inspected on the above-mentioned dates.

BA Research India Ltd is a contract research organization, specialized in conducting Bioavailability, Bioequivalence studies, Clinical Trials (Phase I to IV), Clinical Data Management and Biometrics. BA Research India Ltd is based at three different sites. BA Research India was founded by Mr. Paul Likhari in 2004.

The inspected facility was located at BA Research House. The facility comprised of 2 clinics. The bioanalytical laboratory was located on the fourth floor of the building. The bio-analytical laboratory performed method development, method validation and sample analysis. Quality Assurance/Quality Control and support functions were located on the 3rd floor of facility.

Quality Assurance departments were independent for Clinic & Bioanalytical Laboratory.

A centralized archive was located at the Vadodara site. All documents inspected were retrieved from the Vadodara site. The archive was not inspected.

Uninterrupted power supply to instruments was ensured through a diesel power DG Set (400 KVA) back up system.

History of WHO and/or regulatory agency inspections

This site was not previously inspected by WHO.

CRO facilities were approved by Drug Controller General of India (DCGI).

The facility has been inspected by:

- 2006 - AFSSAPS (Clinic, Laboratory & Statistics)
- 2007 May - USFDA (Clinic)
- 2007 September - USFDA (Clinic, Laboratory & Statistics)
- 2009 - SA MCC (Clinic, Laboratory & Statistics)
- 2010 - USFDA (Laboratory & Statistics)

The diagnostic laboratory was accredited by the College of American Pathology in September 2007 and September 2009.

Focus of the inspection

The inspection focused on the bio-equivalence study conducted for the product Didanosine 400mg capsules. The inspection covered the relevant sections of the WHO GCP, GLP and related texts, including the WHO guidance for organizations performing in vivo bioequivalence studies.

Inspected Areas and documents reviewed

The inspectors reviewed various documents which included SOPs such as:

- "Subject check in check out"
- "Procurement and handling of investigational products"
- "Dispensing of investigational products"
- "Collection of blood samples"
- "Handling of biological samples from collection to storage"
- "Archiving, retention and retrieval of records and data"
- "Emergency monitoring of freezers and refrigerators"
- "Sample analysis (chromatographic)"
- "Security of computer system"
- "Backup, archiving, retrieval and re-archival of electronic data"

Day 1:

The following documents were reviewed:

- Contract between the sponsor and BA (study specific)
- Project Contract with the sponsor
- Master service agreement
- Job description for the Principal Investigator
- "Break-up" compensation policy approved by IEC
- Compensation list and payment slip
- ICF for all subjects signatures were cross checked with subject arrival records
- Training records for :
 - Principal investigator
 - Protocol training records for all staff members who took part in the study
 - Person who was involved in dosing
 - Persons who were involved in dispensing
 - Nurse
 - Contracted medical doctor
 - Study personnel assignment record
- ICF shipping letter to the ICE
- Monitor report
- IEC
- Minutes of IEC meeting

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- IEC chairman CV and training
- Insurance
- Pre screening information
- Protocol:
 - ICF for screening - English and Gujarati languages
 - ICF for study - approved by IEC English and Gujarati languages
 - ICF for all subjects (signatures were cross checked with subject arrival records - ID)
 - Compensation list, payment slip
- CRF for the number of subjects, including the following data for those CRFs:
 - Medical screening records
 - Pathology
 - ECG - pre study
 - X-ray films
 - Birth certificates
 - Dosing vs randomization list
 - Meal records
- Investigational products documentation:
 - Randomization list
 - Proof of purchase of reference product (Invoice)
 - Letter from sponsor - sending of reference and test products
 - Acknowledgement letter of receiving the samples
 - Investigational product receipt
 - Dispensing record - Dispensing check list
 - Dispensing labels
 - Drug accountability form
 - CoA's - for the reference and test products
- Vacutainer labels

After the review of the above-mentioned documents, the clinical unit was inspected. Various areas were visited including the former screening area, emergency room, wards, offices, change rooms and pharmacy.

The pharmacy

The access to the pharmacy was controlled. There were two sets of keys. One was held with QA and one by the pharmacist. It was necessary to use both keys and access card to open the pharmacy. Pharmacy was equipped with, humidity control oven (22.5±2 °C) and refrigerator (2-8 °C) to store IP as per the storage condition. Entrance to the dispensing and sample storage room was via step-over bench. Reconciliation was carried out for investigational products - test product and reference product. The temperature in the pharmacy and humidity control oven and refrigerator was recorded continuously using chart recorders; and also manually once per day.

The following documents were reviewed in the pharmacy:

- Entrance card
- Investigational product samples entrance log book
- Investigational product samples log book "in - out"

Intensive Care Unit (ICU)

The ICU was equipped with all necessary instruments such as a defibrillator, suction machine, cardio monitor and oxygen. All equipment had log books. Medicines inventory was updated before every study. On spot check, the medicines expiry dates were within the limits.

Day 2

The following documents were reviewed:

- Temperature mapping report for specific deep freezer and calibration certificate of digital thermometer, thermometer and calibration of data logger
- Log book for samples in-out to the freezer
- Shipment log for biological samples
- Sample receipt form
- Sample receiving log book (clinic - laboratory)
- Laboratory note book for specific freezer
- Shipment log for biological samples from the CRO to the sponsor. This shipment log included:
 - Sample collection log
 - Shipment details
 - Sample details
- Project specifications for BA analysis.
- CV and training records for study director
- Training records of person involved in the analytical method validation and person involved in subject analysis
- Sponsor post study monitoring report and post study audit report

The following documents were checked for the analytical method validation:

- Validation specification
- Validation control form
- Research & Development book for Didanosine
- Refrigerator stock solution stability
- Selectivity:
- Back up calculations (precision and accuracy) were carried out for the number of QC's used during method validation :

The concentrations were calculated properly, no remarks were made by the inspectors.

The following other documents were checked for the study:

- Analytical procedure sheet (solid phase extraction) - records of study data. No remarks were made by the inspectors.
- Pre-study validation. No remarks were made by the inspectors.

- Technicians validation. No remarks were made by the inspectors.
- Sample analysis.
 - Concentration was back calculated for a number of subjects. No remarks were made by the inspectors.

A number of pipette calibration records were checked. No remarks were made by the inspectors.

Laboratory tour

The samples were stored in a walk in freezer (- 20 °C) and deep freezer (-70 °C). There were separate storage rooms for reagents and laboratory glassware and plastic materials. Deionized water was generated using Milipore equipment.

Balance room

Balance daily verification was carried out using calibrated standard weights. Before every weighing the standard weight which was close to the analysis weight was used to check the performance of the balance. Balances were calibrated by the external agency once per year. Disposable weighing pans were used. Balance calibration and standard weights calibration certificates were checked. No remarks.

Working standards were stored in a locked, temperature controlled fridge and were issued for analysis by project manager. Reference standard tracking logs were reviewed for the study and method validation.

Day 3

Source data (soft copy of chromatograms) for a number of samples were compared on PC screen with corresponding data from electronic files generated by the analytical software (analyst) along with audit trail.

Sigma facility.

Screening from inspected facility was moved to the Sigma facility.

The CRO had an OVIS Online volunteer information system. The system was operating in Gujarat state and the main CROs were connected to the system. Data was entered to the system by CRO personnel after the first dosing. The OVIS system was maintained by a third party, and the server was located abroad.

For studies - subjects only from Gujarat state were enrolled.

During the inspection, the current screening procedure was checked. Subjects were identified by fingerprints (biometric device). The CRO subject information system was challenged. No remarks were made by the inspectors.

Server room HQ.

Each site had its own independent server. The server was password protected.

Backup was carried out daily, weekly and monthly.

THE PROTOCOL

The Protocol was found in general to be acceptable.

PROTECTION OF TRIAL SUBJECTS

Protection of the volunteers was found to be acceptable, Helsinki declaration was followed, informed consents were within the requirements.

RESPONSIBILITIES OF THE INVESTIGATOR

Responsibilities of the investigator were defined, selection of subjects were done in accordance with defined procedures. Subjects were properly informed, ICF's were signed by the volunteers. The study protocol was reviewed and approved by the ethics committee. The Monitor performed a site audit and monitoring reports were available.

Pharmaceutical products were handled appropriately.

The trial site had adequate premises.

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.

RESPONSIBILITIES OF THE MONITOR

Case report forms were appropriate.

MONITORING OF SAFETY

Subject safety was monitored. There were no adverse events during this study.

RECORD-KEEPING AND HANDLING OF DATA

Handling of data was considered acceptable. Study records were stored in the CRO archive in Vodadora.

HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

Supply of products and storage of products as well as labeling and packaging were found in general to be acceptable. Dispensing documentation should be improved in accordance with GMP principles, see observation below.

QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

The quality assurance was consistent and acceptable.

Part 3: Conclusion

Based on the areas inspected, the people met and the documents reviewed, and considering the findings of the inspection of the above-mentioned study (BBRC/EX/10/001) An Open Label, Randomized, Two Period, Two Treatment, Two Sequence, Crossover, Balanced, Single Dose Comparative Evaluation Of Relative Bioavailability Of Didanosine Delayed Release Capsules 400 mg comparing with that of 'VIDEX[®]EC' Delayed Release Capsules 400 mg, made in Bristol-Myers Squibb Company, Princeton, NJ 08543, USA (containing Didanosine Delayed Release Capsules 400 mg) in Healthy Adult Human Subjects Under Fasting Conditions in India, conducted at BA Research India Ltd., BA Research House, Opp. Pushparaj Towers Nr. Judges Bungalows Bodakdev, Ahmedabad-380 054 India, India was considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP guidelines.

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
www.who.int/prequal

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