



WHO PUBLIC INSPECTION REPORT

(WHOPIR)

Bio-Equivalence Study

Part 1: General information

WHO product numbers covered by the inspection	<ol style="list-style-type: none"> 1. HA414: Tenofovir disoproxil fumarate/Lamivudine 300/300mg tablets. 2. HA433: Lamivudine/Nevirapine/Zidovudine 30/50/60mg tablets 3. HA436: Abacavir Sulfate/Lamivudine/Zidovudine 60/30/60mg tablets, (<i>biowaver based on BE study for Abacavir Sulfate/Lamivudine/Zidovudine 300/150/300mg tablets which was inspected</i>). 4. HA444: Tenofovir Disoproxil Fumarate / Emtricitabine / Efavirenz 300/200/600mg tablets.
Study number	<ol style="list-style-type: none"> 1. HA414: 06-VIN-171 2. HA433: 07-VIN-123 3. HA436: 07-VIN-154 4. HA444: 06-VIN-169
Title of the study	<ol style="list-style-type: none"> 1. HA414: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of combined Tenofovir disoproxil fumarate 300mg and Lamivudine 300mg tablets of Matrix Laboratories Limited (India) and individual Viread[®] (Tenofovir disoproxil fumarate) 300mg of Gilead Sciences, USA and Epivir[®] (Lamivudine) 300mg tablets of GlaxoSmithKline, USA in healthy human adult male subjects, under fed conditions 2. HA433: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Lamivudine plus Nevirapine plus Zidovudine 30/50/60mg tablets of Matrix Laboratories Limited, India (two tablets) and Epivir[®] Oral Solution containing 10mg/mL of Lamivudine of GlaxoSmithKline, USA (as 60mg dose), Viramune[®] Oral Suspension containing 50mg/5mL of Nevirapine (as nevirapine hemihydrate) of Boehringer Ingelheim Pharmaceuticals, Inc., USA (as 100mg dose) and Retrovir[®] Syrup containing 50mg/5mL of Zidovudine of GlaxoSmithKline, USA (as 120mg dose) in healthy adult human subjects, under



	<p>fasting conditions.</p> <p>3. HA436: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Abacavir sulfate 300mg, Lamivudine 150mg and Zidovudine 300mg tablets of Matrix Laboratories Limited, India and Trizivir® (Abacavir sulfate / Lamivudine / Zidovudine) 300/150/300mg tablets of GlaxoSmithKline, USA in healthy adult human subjects, under fasting conditions.</p> <p>4. HA444: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Tenofovir Disoproxil Fumarate 300mg and Emtricitabine 200mg and Efavirenz 600 mg tablets of Matrix Laboratories Limited (India) and ATRIPLA™ (Tenofovir Disoproxil Fumarate 300mg and 200mg Emtricitabine and Efavirenz 600mg) tablets of Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A. in healthy human adult male subjects, under fasting conditions.</p>
<p>Clinical Part of the study: Name and address of the organization</p>	<p>Veeda Clinical Research Pvt. Ltd. Shivalik Plaza-A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India. Phone: +91-79-30013000, Fax: +91-79-30013010</p>
<p>Name and email address of contact person (Clinical part)</p>	<p>Principal Investigator :</p> <ol style="list-style-type: none"> 1. HA414: Dr. Dharmesh Domadia M.D. 2. HA433: Dr. Jinesh Shah M.D. 3. HA436: Dr. Dharmesh Domadia M.D. 4. HA444: Dr. Dharmesh Domadia M.D.
<p>Bio-analytical laboratory: Name and address</p>	<ul style="list-style-type: none"> • <u>HA414, HA433 and HA436:</u> Matrix Laboratories Limited IInd Floor, Cresscent's Krishna Metropolis, Near Poulomi Hospital, A.S. Rao Nagar, Sainikpuri-ECIL Main Road, Secunderabad - 500 062, India. Tel: + 91 40 27138563 Fax: + 91 40 27138562 E-mail: Ramakrishna.bangaru@matrixlabsindia.com • <u>HA444:</u> Veeda Clinical Research Pvt. Ltd. Shivalik Plaza-A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India. Phone: +91-79-30013000,



	Fax: +91-79-30013010 E-mail: rajendra.prasad@veedacr.com
Name and email address of contact person (Bio-analytical part)	Bioanalytical Investigator: 1. HA414, HA433 and HA436: Mr. Amarnath Jaiswal, Matrix Laboratories Limited. 2. HA444: Mr. Rajendra Prasad, Veeda Clinical Research Pvt. Ltd.
Name and address of the Sponsor	Matrix laboratories Ltd , 1-1-151/1, 4 th Floor, Sairam Towers, Alexander Road, Secunderbad, 500 003, Andhra Pradesh, India
Name and email address of contact person (Sponsor)	Dr. Ramakrishna Bangaru, Vice President E-mail: Ramakrishna.bangaru@matrixlabsindia.com
Date of inspection	Veeda: 20 - 21 July 2009 Matrix: 22 - 23 July 2009.

Part 2: Summary

General information about the site(s)

(a) Veeda Clinical Research Pvt. Ltd

The site inspected was called **Veeda Clinical Research Private Limited, Shivalik Plaza-A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India** (hereafter referred to as **Veeda**) where the clinical part of the four studies (for **HA414, HA433, HA444 and to support a bio-waiver for HA436**) and the bioanalytical study of one of the studies (for **HA444**) reviewed during this inspection were conducted. According to the presentation at the opening meeting of the inspection, the company was incorporated in 2004 and started operating as an independent Clinical Research Organization (CRO) at this site in 2005. The site had screening (1,000sq.ft), clinical (21,000sq.ft, 116 beds) and bioanalytical (6000sq.ft) facilities spread on a total area of 43,000sq.ft with the following sections:

- 2nd floor: Bioanalytical laboratory (BAL) and administration.
- 3rd floor:
 - Clinic 1: with 26 beds and 1 special care (ICU) bed.
 - Clinic 2: with 36 beds and 2 special care (ICU) beds.
- 4th floor:
 - Clinic 3: with 42 beds and 2 special care (ICU) beds.
 - Clinic 4 (Phase-1clinic): with 12 monitored beds and 2 special care (ICU) beds.
- Wing B: screening area.

Each clinic was self-contained with a phlebotomy and sample processing and storage facilities. There were two pharmacies one on the 3rd floor and another on 4th floor. The pharmacy on the 3rd floor which was visited had a pharmaceutical refrigerator, a walk-in humidity chamber and dispensing facilities for storage and dispensing of investigational products (IPs). There was an in-house kitchen, dining facilities and dietician to provide meals for the study subjects.

The BAL had 12 LC-MS/MS, 2 HPLCs, automatic sample processing equipment (centrifuges, solid phase and liquid-liquid extractions, evaporators, fume hoods, etc) and freezers of different ranges (20^oC - 70^oC) for sample storage.

The screening section wing B had a **Biometrics database**, a computer-based method for uniquely recognizing and screening volunteers and study subjects based upon one or more of their intrinsic physical traits (e.g. fingerprint, face recognition). It was stated that Veeda had 8700 volunteer database. It was also linked to the Online Volunteer Information System (OVIS) which served several CROs in Ahmedabad to ensure that volunteers observed the period within which they may not participate in a new study after participating in one.

(b) Matrix Laboratories Limited, Clinical Research Centre

The bioanalytical part of three of BE studies (**HA414, HA433 and to support bio-waiver for HA436**) reviewed was conducted at **Matrix Laboratories Limited, IInd Floor, Crescent's Krishna Metropolis, Near Poulomi Hospital, A.S. Rao Nagar, Sainikpuri-ECIL Main Road, Secunderabad-500 062, India**. However, this centre was closed and in June 2008 a new centre was established at the site that was inspected located at **Matrix Laboratories**

Limited, Clinical Research Centre, Saradhi Chambers, A-4 Rukminipuri, Near Poulomi Hospital, Main Road, Dr. A.S. Rao Nagar, Hyderabad-500 062, India (hereafter referred to as Matrix BAL).

Matrix BAL only operated a Bioanalytical Laboratory with an area of 25,000sq.ft, 10 LC-MS/MS, 8 HPLCs, 5 centrifuges, 14 extractors (solid-phase and liquid-liquid), 24 deep different freezers [-20⁰C(4), -30⁰C(1), -40⁰C(10) to -70⁰C(9)], 6 pharmaceutical refrigerators (2⁰C - 8⁰C), 6 sample concentrators (Nitrogen Evaporators), 3 balances, 3 fume hoods and a staff of 42 in bio-analysis, 7 in pharmacokinetics and 4 in Quality Assurance.

History of WHO and/or regulatory agency inspections

(a) Veeda Clinical Research Pvt. Ltd

WHO prequalification had on two previous occasions (July 2007: HA393 and June 2008: HA404) inspected studies conducted at Veeda India. This inspection focused on the clinical part of the four studies outlined above and bioanalytical part for product HA444.

Veeda had been inspected and approved by the Drug Controller General of India (DCGI).

According to the presentation by the company, the CRO or studies conducted thereby had been inspected and approved by ENVISA, Brazil (2006, 2007 and 2008: CRO), USFDA (2007, 2008 and 2009: 8 studies) and MHRA (2007: CRO).

(b) Matrix Laboratories Limited, Clinical Research Centre

WHO Prequalification had previously inspected Matrix BAL and studies whose samples were analysed at this site (January 2008 for HA392; and in June 2008 for HA404 and HA411). This inspection focused on **HA414, HA433 and HA436**.

According to the presentation by the company, studies conducted at BAL had been inspected and approved by USFDA (September 2007, March 2008 and June 2008) and Thai FDA (December 2007). The following changes had been implemented since the last inspection:

- Freeze Thaw (FT) stability both at -20⁰C and -70⁰C.
- Quality control/Calibration curve (QC/CC) sample accuracy and precision including all the values in global calculation.
- Clinical study monitoring staff had been increased.

Focus of the inspection

The inspection at Veeda focused on the clinical part of the bio-equivalence studies conducted for the products **HA414** (Tenofovir disoproxil fumarate/Lamivudine 300/300mg tablets), **HA433** (Lamivudine/Nevirapine/Zidovudine 30/50/60mg tablets), **HA444** (Tenofovir Disoproxil Fumarate/Emtricitabine/Efavirenz 300/200/600mg tablets) and Abacavir Sulfate/Lamivudine/Zidovudine 300/150/300mg tablets to support a bio-waiver for **HA436** (Abacavir Sulfate/Lamivudine/Zidovudine 60/30/60mg tablets) and the bioanalytical part for **HA444**. The bioanalytical part for **HA414, HA433 and to support bio-waiver for HA436** were conducted at Matrix CRO. 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 (at Veeda)

On arrival, the inspectors were directed into the conference room, introduced themselves and exchanged business cards. They explained the procedure for WHO Prequalification Programme, the procedures and standards used for inspection including the WHO Public Inspect Report (WHOPIR) and Notice of Concern (NOC) and elaborated on the tentative inspection plan. After confirming the inspection plan, the company made a presentation about the company, the site and the studies to be inspected. The presentation highlighted the history of establishment, capacities, facilities and the history of regulatory inspections. A copy of the presentation was obtained and will be filled in the company file. A copy of the Quality manual for Veeda was also provided.

The following documentation for all BE studies (**HA414, HA433 HA436 and HA444**) were reviewed:

- Relation between sponsor and CRO (contract, monitoring).
- Ethics committee composition, procedures (protocol, ICF, CRF, translations, amendments, correspondences, minutes and signatures).
- Pre-study meeting and training records.
- Screening and procedures of administration of informed consent.
- Randomization procedures.
- Case report forms and other related documents for selected subjects.
- Documentation related to sourcing, shipment, receipt, storage and control of Investigational Products (IPs).
- Control of meals and feeding of subjects.
- Dispensing and dosing operations.
- Blood sample handling, storage and transfer from CRO to BAL.
- Monitoring of adverse events, withdrawal of subjects.
- Facilities in the Pharmacy department.
- Relationship between final report and raw data.

At the end of the day, the team reviewed progress of the activities of the day, gave feed back, received reactions from the management of the company and agreed on the tentative programme for the next day.

Day 2 (at Veeda)

The following areas of Bioanalytical study of **HA444** were reviewed:

- Documentation related to method validation with focus on Efavirenz (preparation of stock solution, dilutions, preparation of QCs and CCs, log books for placement and withdrawal of sample from deep freezer, runs for precision and accuracy and long term stability).
- Sourcing and documentation of reference and internal standards.

- Analysis of study samples with focus on Tenofovir and Efavirenz for selected study subjects, particularly for repeated and rejected runs.
- Preparation of stock solution for Tenofovir.
- Review of runs with marginally passing QCs.

At a half past mid-day, the team reviewed the activities of the two days, gave feed back and received reactions from the management of the CRO. They left for the airport and to Hyderabad for inspection of the Matrix BAL.

Day 3 (at Matrix BAL)

On arrival at Matrix BAL, the inspectors were directed into the conference room, introduced themselves and exchanged business cards. They explained the procedure for WHO Prequalification Programme, the procedures and standards used for inspection including the WHO Public Inspect Report (WHOPIR) and Notice of Concern (NOC) and elaborated on the tentative inspection plan. After confirming the inspection plan, the company made a presentation about the company and the site to be inspected. The presentation highlighted the history and reasons for the establishment of Matrix BAL, organization, capacities, facilities, quality management systems, available bio-analytical methods and the history of regulatory inspections. A separate presentation was made for each of the studies to be inspected. A copy of each of the presentations was obtained and will be filled in the company file.

The following areas of Bioanalytical study of **HA414** and **HA433** were reviewed:

- Documentation related to method validation (preparation of stock solution, dilutions, preparation of QCs and CCs, log books for placement and withdrawal of sample from deep freezer, runs for precision and accuracy and long term stability).
- Analysis of study samples for a selected study subjects, particularly for repeated and rejected runs.
- Preparation of stock solutions for sample analysis.
- Reviewed the original chromatograms from the electronic files on the computer software (ANLYST Version 1.4.1) for selected runs, especially rejected runs and those with marginally passing QCs.

At the end of the day, the team reviewed progress of the activities of the day, gave feed back, received reactions from the management of the BAL and agreed on the tentative programme for the next day.

Day 4 (at Matrix BAL)

The following areas of Bioanalytical study of **HA436** were reviewed:

- Documentation related to method validation (preparation of stock solution, dilutions, preparation of QCs and CCs, log books for placement and withdrawal of sample from deep freezer, runs for precision and accuracy and long term stability).
- Analysis of study samples for a selected study subjects, particularly for repeated and rejected runs.
- Preparation of stock solutions for sample analysis.

- Reviewed the original chromatograms from the electronic files on the computer software (ANLYST Version 1.4.1) for selected runs, especially rejected runs and those with marginally passing QCs.

At the end of the day, the team reviewed the activities of the two days, gave feed back and received reactions from the management of the BAL. There was also a wrap up meeting for the entire inspection.

2.1 PROVISIONS AND PREREQUISITES FOR A CLINICAL TRIAL

The studies were conducted to demonstrate bio-equivalence of generic products manufactured by Matrix with innovator products and to support their registration with a number of regulatory agencies, including WHO-PQ and USFDA. All the studies were conducted in duplicate, one as fed and another as a fasting study. Sufficient data was available on site and in the protocols about the investigational products (IPs) to justify and support the study.

According to the records and CVs reviewed, CRO and BAL had adequate numbers of staff with adequate skills to conduct the studies. Both facilities had adequate relevant screening, clinical and analytical facilities for conducting the BE studies. The studies were approved by the relevant independent Ethical Committees and the sites were approved by the Drug Controller General of India.

2.2 THE PROTOCOL

Each study was guided by a protocol which had been signed by both the sponsor and the principle investigator. The protocol was approved by an independent Ethics Committee. The amendments to the protocol were equally signed and approved. The protocols were generally comprehensive and were largely adhered to during the studies. Explanation was received and doubts were cleared on the efficiency and/or independence of signing by both the sponsor and principle investigator, submission to the Independent Ethics Committee and subsequent approval, all on the same day (29.03.2007) in case of protocol No. 06-VIN-171 version 03 for HA414.

2.3 PROTECTION OF TRIAL SUBJECTS

The principles of the Declaration of Helsinki were imbedded in the procedures designed to protect study subjects. The studies were reviewed and approved by an Independent Ethics Committee. There were adequate procedures for screening subjects and ensuring that only those who voluntarily gave informed consent and had not participated in a trial were included in the study. This was supported by biometrics database and the Online Volunteer Information System (OVIS) which served several CROs in Ahmedabad. However, all the ICF reviewed included complex medical terms that could not be easily understood by a lay person.

Although all the BE studies were open label, the confidentiality of the subjects was ensured by reference to their study number instead of their name on most of the study documents and reports.

Study subjects were screened at various stages before, during and after the study to monitor their safety and take appropriate remedial actions. The CRO had adequate emergency facilities and was supported by a standby emergency hospital. Study subjects were covered by an insurance policy and there were well defined policies and procedures for their compensation for participation in the study.

2.4 RESPONSIBILITIES OF THE INVESTIGATOR

The principal investigator (PI) in 3 out of the 4 studies was the same, but the studies did not take place concurrently. According to the CVs, the PIs had the requisite qualifications and experience to conduct the study. The responsibilities of the PI were spelt out in the agreement with the sponsor, the protocol and a number of SOPs. During the inspection, the PIs demonstrated good knowledge and control of the studies.

There was however confusing e-mail correspondence which indicated inadequate coordination between the PI and sponsor during transfer of duplicate samples from Veeda to Manipal AcuNova and subsequently to Matrix BAL. Nevertheless, this discrepancy was later on resolved.

2.5 RESPONSIBILITIES OF THE SPONSOR

The Sponsor for all the studies inspected was Matrix Laboratories Limited and the responsibilities of the sponsor were spelt out in the study agreement between the sponsor and PI/CRO. Matrix had a running agreement with Veeda for which the sponsor regularly assessed the CRO but there was no evidence of study specific evaluation of the CRO by the sponsor. Most of the clinical trial responsibilities had been delegated to the CRO but the sponsor had to provide the investigational products. The contract was not clear about the responsibility for monitoring the study. The funding for the study was transparently covered by the agreement and compensation of study subjects was approved by the Independent Ethics Committee.

2.6 RESPONSIBILITIES OF THE MONITOR

The agreement between the sponsor and the PI/CRO, did not specify how the responsibilities for monitoring were to be executed. There was confusion between the responsibilities of the CRO's quality assurance unit and the monitor appointed by the sponsor. Because of this, it was not possible to establish where the studies were monitored and where the monitors were qualified. Matrix had a running agreement with Veeda for which the sponsor regularly assessed the CRO but there was no evidence of study specific evaluation of the CRO by the monitor.

2.7 MONITORING OF SAFETY OF SUBJECTS

The monitoring of the safety of study subjects was adequately provided in the protocol and CRF. Vital signs and other clinical, radiological, haematological and pathological parameters were monitored at appropriated intervals before, during and after the study. The adverse events encountered in the studies were adequately recorded and managed. Where it was

necessary to withdraw the subject from the study, this was done and adequately documented in the report.

2.8 RECORD-KEEPING AND HANDLING OF DATA

Due to time constraints, the procedures for archiving were not evaluated. Nevertheless, except for some documentation related with the deliberations of the Independent Ethics Committee and transfer of some of the duplicate samples to the BAL, most of the documentation that was requested for was provided in reasonable time.

2.9 STATISTICS AND CALCULATIONS

The design of the bio-equivalence studies was a randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study. The parameters monitored were C_{max} , AUC_{0-t} & AUC_{0-inf} and the 90% Confidence Interval acceptance criteria was 80.00% – 125.00%. Selected recalculations confirmed the results challenged.

One of the studies was repeated with a bigger sample [HA436: increased from 48 subjects in 07-VIN-005 to 60 subjects in 07-VIN-154] following failure of C_{max} with respect to one of the analyte (Zidovudine). Although adequate and acceptable justification for this repetition was available, it should have been included in the repeated study protocol and report at least as background information.

Bio-analysis of all samples was repeated at the sponsor's owned BAL (Matrix BAL) using duplicate samples following concerns about the, practices, results and reproducibility of the method used by the original independent BAL (Manipal AcuNova). There was a full investigation of the problem and adequate justification of the repeat analysis was documented in version No.02 of the report. There was however no evidence that the protocol was amended and the change in BAL (from Manipal AcuNova to Matrix) approved by the IEC since the BAL was specifically mentioned in the approved protocol.

Computer-based software was used to analyse data from bio-analysis. The computers in use were checked for password protection, protection of computer dates and activation of the audit trail and nothing adverse was observed.

2.10 HANDLING OF AND ACCOUNTABILITY FOR PHARMACEUTICAL PRODUCTS

There was generally adequate accountability of the investigational products in form of documentation for purchase, shipment, receipt, storage, dispensing, administration and stock reconciliation. Both the supplied and dispensed IPs were appropriately labelled. The storage and handling facilities were generally acceptable.

2.11 ROLE OF THE DRUG REGULATORY AUTHORITY



The sites had been inspected and licensed by the Drug Control General of India or the state authorities and necessary authorization to import the investigational products had been obtained. Representatives of the DCGI were present during inspection at both sites.

2.12 QUALITY ASSURANCE FOR THE CONDUCT OF A CLINICAL TRIAL

Veeda CRO and Matrix BAL each had a quality assurance unit supported with a number of SOPs. Selected study related SOPs were reviewed but most SOPs were not reviewed in detail because they had been reviewed during previous inspections.

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 studies:

1. **06-VIN-171**(for **HA414**): A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of combined Tenofovir disoproxil fumarate 300mg and Lamivudine 300mg tablets of Matrix Laboratories Limited (India) and individual Viread[®] (Tenofovir disoproxil fumarate) 300mg of Gilead Sciences, USA and Epivir[®] (Lamivudine) 300mg tablets of GlaxoSmithKline, USA in healthy human adult male subjects, under fed conditions
2. **07-VIN-123** (for **HA433**): A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Lamivudine plus Nevirapine plus Zidovudine 30/50/60mg tablets of Matrix Laboratories Limited, India (two tablets) and Epivir[®] Oral Solution containing 10mg/mL of Lamivudine of GlaxoSmithKline, USA (as 60mg dose), Viramune[®] Oral Suspension containing 50mg/5mL of Nevirapine (as nevirapine hemihydrate) of Boehringer Ingelheim Pharmaceuticals, Inc., USA (as 100mg dose) and Retrovir[®] Syrup containing 50mg/5mL of Zidovudine of GlaxoSmithKline, USA (as 120mg dose) in healthy adult human subjects, under fasting conditions.
3. **07-VIN-154** (for a bio-waiver for **HA436**): A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Abacavir sulfate 300mg, Lamivudine 150mg and Zidovudine 300mg tablets of Matrix Laboratories Limited, India and Trizivir[®] (Abacavir sulfate / Lamivudine / Zidovudine) 300/150/300mg tablets of GlaxoSmithKline, USA in healthy adult human subjects, under fasting conditions.
4. **06-VIN-169** (for **HA444**): A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Tenofovir Disoproxil Fumarate 300mg and Emtricitabine 200mg and Efavirenz 600 mg tablets of Matrix Laboratories Limited (India) and ATRIPLA[™] (Tenofovir Disoproxil Fumarate 300mg and 200mg Emtricitabine and Efavirenz 600mg) tablets of Bristol-Myers Squibb and Gilead Sciences Inc, U.S.A. in healthy human adult male subjects, under fasting conditions,

were considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP at:

- **Veeda Clinical Research Private Limited, Shivalik Plaza-A, Near I.I.M., Ambawadi, Ahmedabad – 380 015, India** where the clinical part of the four studies (for **HA414**, **HA433**, **HA444** and to support a bio-waiver for **HA436**) and the bio-analysis for one of the studies (for **HA444**) were conducted.
- **Matrix Laboratories Limited, Clinical Research Centre, IInd Floor, Cresscent's Krishna Metropolis, Near Poulomi Hospital, A.S. Rao Nagar, Sainikpuri-ECIL Main Road, Secunderabad-500 062, India** where the bio-analysis for three of BE studies (for **HA414**, **HA433** and to support bio-waiver for **HA436**) was conducted. Please note that this BAL was letter transferred to **Saradhi Chambers, A-4 Rukminipuri, Near Poulomi Hospital, Main Road, Dr. A.S. Rao Nagar, Hyderabad-500 062, 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.