

Prequalification of Medicines Programme
WHO PUBLIC INSPECTION REPORT
Bio-Equivalence Study

Part 1: General information

Name of organization	Ranbaxy Laboratories Limited, Department of Clinical Pharmacology and Pharmacokinetics
Physical address	Plot No. GP-5, Sector 18, HSIDC, Old Delhi-Gurgaon Road, Gurgaon 122 015, Haryana, India
Postal address	Same as above
Telephone number	+91 124 423 1001
Fax number	+91 124 423 1002
Summary of activities	Performance of bioequivalence trials (bioanalytical part only)
Date of inspection	24 - 26 August 2009
Scope of the inspection	Study specific GCP inspection
Programme	Prequalification of Medicines Programme
WHO reference number Study	HA423 Study No. 124_TENOF_07 Title: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioavailability study comparing tenofovir disoproxil fumarate tablets 300 mg of Ranbaxy Laboratories Limited, with Viread [®] tablets (containing tenofovir disoproxil fumarate 300 mg) of Gilead Sciences Inc., in healthy, adult, male, human subjects under fasting condition. Clinical phase: 17 August - 05 September 2007 Bioanalytical phase: 15 to 20 October 2007
Investigational product	Tenofovir disoproxil fumarate 300 mg tablets Manufactured by Ranbaxy Laboratories Limited, India Batch number: 1793957 Expiry date: June 2009
Reference product	Viread [®] (Tenofovir disoproxil fumarate) 300 mg tablets Manufactured for Gilead Sciences Inc., Foster City, CA, 94404, USA. Made in Canada. Lot number: V0112A307 Expiry date: May 2008
Sponsor	Ranbaxy Laboratories Limited, India
WHO reference number	HA449



Study	<p>Study No. 201_EFAET_08</p> <p>Title: An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, crossover bioequivalence study comparing fixed dose combination tablets containing Efavirenz 600 mg, Emtricitabine 200 mg and Tenofovir disoproxil fumarate 300 mg (300 mg of Tenofovir disoproxil fumarate which is equivalent to 245 mg of Tenofovir disoproxil) of Ranbaxy Laboratories Limited with ATRIPLA™ tablets (containing Efavirenz 600 mg, Emtricitabine 200 mg and Tenofovir disoproxil fumarate 300 mg) of Bristol Myers-Squibb and Gilead Sciences, in healthy, adult, male, human subjects under fasting condition.</p> <p>Clinical phase: 30 January - 10 March 2008 Bioanalytical phase: 24 April - 20 May 2008.</p>
Investigational product	<p>Efavirenz 600 mg, Emtricitabine 200 mg and Tenofovir disoproxil fumarate 300 mg tablets Manufactured by Ranbaxy Laboratories Limited, India Batch number: 1850824 Expiry date: November 2009</p>
Reference product	<p>Atripla™ 600 mg / 200 mg / 300 mg tablets Manufactured for Bristol Myers-Squibb and Gilead Sciences LLC, Foster City, CA 94404, USA. Made in Canada. Batch number: V0129A007 Expiry date: May 2008</p>
Sponsor	<p>Ranbaxy Laboratories Limited, India</p>

Part 2: Summary

Ranbaxy Laboratories Limited (hereafter referred to as Ranbaxy) located in Gurgaon, India, were inspected by a WHO prequalification inspection team on the above mentioned dates.

About the company and the facilities of the trial

A brief presentation of the structure and activities of the Department of Clinical Pharmacology and Pharmacokinetics was made at the opening meeting of the inspection.

Trial No. 124_TENOF_07 was performed at an older facility of Ranbaxy, located Plot No. 20, Sector 18, Udyog Vihar Industrial Area, Gurgaon 122 015, Haryana, India. This facility was not visited during this inspection.

The clinical part of the two trials inspected was conducted at two different clinical pharmacology units of Ranbaxy. These two clinics had been previously inspected by the WHO.

On the date of the inspection the facilities included the following:

- 8 sample processing rooms, each placed under the supervision of a laboratory supervisor heading a team of analysts, using equipment dedicated to each team;
- 11 LC/MS/MS rooms, with a total of 22 LC/MS/MS instruments (MDS Sciex API 3000, 3200 and 4000; one Micromass Quattro Premier);
- a balance room;
- two freezer rooms, with a total of 8 -70°C deep freezers and 4 -20°C cold rooms;
- the offices of the chromatogram review group.

History of inspections (WHO, regulatory authorities etc.)

Ranbaxy had already been inspected previously by the WHO in 2005 and 2007. (The Clinical Pharmacology and Pharmacokinetics department of Ranbaxy Laboratories Limited located at Plot No. 20, Sector 18, Udyog Vihar Industrial Area, Gurgaon 122 015, Haryana, was inspected in 2007 for the first time).

They were also previously inspected by the US FDA, Afssaps (France) and the MHRA (UK).

Purpose of the inspection

The purpose of the inspection was to verify the quality and integrity of the data and information for bioequivalence study reports submitted by the sponsor to WHO, and to assess whether the studies were conducted in compliance with the protocols, Good Clinical Practice (GCP) and Good Laboratory Practice (GLP).

Focus of the inspection

The inspection focused on the bioanalytical part of two specific bioequivalence trials: 124_TENOF_07 (HA423) and 201_EFAET_08 (HA449).

On the first day of the inspection, the inspectors introduced themselves. Ranbaxy staff introduced themselves and after exchanging business cards, Ranbaxy staff made a short presentation. The facilities were then visited. During the visit the remaining plasma samples of study No. 201_EFAET_08 were shown to the inspectors.

On the first day of the inspection, the inspectors checked the documentation and raw data relating to the following activities for the validation of the bioanalytical method used for the simultaneous determination of emtricitabine and efavirenz:

- preparation of stock solutions and of calibration and quality control (QC) samples, on 28 February 2008. Calibration and QC samples were prepared from separate stock solutions. The inspectors recalculated the nominal concentration of the calibration and QC samples, and checked the number of aliquots prepared. They reviewed the documentation relating to the checks of the pipettes used for this preparation, performed on the same day. The batches of EDTA blank plasma used, procured from Ranbaxy's clinical pharmacology unit at Majeedia Hospital, were documented in a matrix usage record logbook. Bleed sheets were available to document the collection of these plasma samples;

- second run for the determination of the precision and accuracy of the method. The inspectors checked all chromatogram integrations, the audit trail settings and the contents of the audit trail, and the nominal concentration of the calibration samples. They recalculated manually the efavirenz concentrations. They compared all efavirenz and emtricitabine concentrations with those reported in the validation report;

- matrix effects. The inspectors checked the integration of all chromatograms, the audit trail settings and the contents of the audit trail. They compared all emtricitabine concentrations with those reported in the validation report. They checked the variability of peak areas;

- long-term stability in plasma for 154 days. The inspectors recalculated the nominal concentration of the fresh calibration samples used, and compared the emtricitabine and efavirenz concentrations with those reported in the validation report;

- incurred sample reanalysis. The inspectors asked for additional results obtained by Ranbaxy but not reported (samples reanalysed for one of the analytes due to the failure of the initial analytical run for that analyte, for which a second valid result was obtained for the second analyte during the reanalysis as the calibration and QC samples contained both analytes, and samples selected for incurred sample reanalysis for one of the analytes but not for the other).

On the second day of the inspection the inspectors checked the documentation and raw data relating to the preparation of the calibration and QC samples for the simultaneous determination of emtricitabine and efavirenz for study No. 201_EFAET_08. They checked which analytical run was performed on which LC/MS/MS instrument, with which subject samples, at what date, and the final acceptance or rejection of these analytical runs. Rejected analytical runs were identified in the analytical report. The inspectors also reviewed the results of investigation batches analysed after the failure of several analytical runs. They reviewed the documentation relating to the analysis of the samples of subject No. 03, of subject No. 40, and to the reanalysis of samples. For these 3 runs they systematically checked all chromatogram integrations, the variability of the internal standard response, the absence of time gaps in the injection sequence, the contents of the audit trail, and compared all concentrations with those reported in the trial report.

In addition :

- for subject No. 03, they checked the reason for the exclusion of a calibration sample for efavirenz. They recalculated all efavirenz concentrations, and the concentration of the calibration and QC samples for emtricitabine;

- for subject No. 40, they recalculated the concentration of all QC samples for emtricitabine and efavirenz;

- for the repeat analysis, they recalculated the concentration of all QC samples for emtricitabine and efavirenz and the concentration of a few samples analysed with a 1:2 dilution.

On the second day of the inspection the inspectors also checked the documentation and raw data relating to the preparation of the calibration and QC samples for the determination of tenofovir for study No. 201_EFAET_08. They checked which analytical run was performed on which LC/MS/MS instrument, with which subject samples, at what date, and the final acceptance or rejection of these analytical runs. Rejected analytical runs were identified in the analytical report. The inspectors also reviewed the results of investigation batches analysed after the failure of several analytical runs. They reviewed the documentation relating to the analysis of the samples of subject No. 03, and of subject No. 40. For these two runs they systematically checked all chromatogram integrations, the variability of the internal standard response, the absence of time gaps in the injection sequence, the contents of the audit trail, the nominal concentration of the calibration samples used for the calculations, and compared all concentrations with those reported in the trial report. In addition they recalculated all concentrations in the run for subject No. 03, and the concentrations of all QC samples for subject No. 40.

On the third day of the inspection the inspectors checked the documentation and raw data relating to the preparation of the calibration and QC samples for the determination of tenofovir for study No. 124_TENOF_07. They reviewed the documentation relating to the analysis of the samples of subjects No. 10, 13 and 15. For these 3 runs they systematically checked all chromatogram integrations, the variability of the internal

standard response, the absence of time gaps in the injection sequence, the contents of the audit trail, and compared all concentrations with those reported in the trial report.

In addition :

- for subject No. 13, they checked the nominal concentration of the calibration samples used for the calculations, and they recalculated all tenofovir concentrations;

- for subject No. 15, they checked the reason for the exclusion of two calibration samples, and they recalculated the concentration of all QC samples;

- for subject No. 10, they checked the reason for the exclusion of one calibration sample, and they recalculated the concentration of all QC samples.

In addition the inspectors reviewed the contents of the audit trail for all other subjects, and checked the reason for the exclusion of a calibration sample for subject No. 07. They checked the records of the controls of pipettes No. AP171 and AP190, used for sample processing (last control before and first control after the study). They checked the controls of the balance for the period when it was used for the preparation of the stock solutions used to spike the calibration and QC samples. They reviewed the synopsis of the report of study No. 132_TENOF-07 (fed bioequivalence study on the same tenofovir tablets), which had not been submitted to the WHO.

The inspectors reviewed the temperature records of the freezer used to store the subject samples, for the duration of their storage between their receipt at the laboratory and their analysis, for both studies inspected.

The inspectors also asked for a demonstration and further explanations regarding the data transfer in PDF format between the Analyst software, used for chromatogram acquisition and integration and for concentration calculations, and the NuGenesis software used for data review and validation. All chromatograms reviewed during the inspection were reviewed using the Analyst software.

The inspectors took copies of Addendum IV to the report of the validation of the tenofovir bioanalytical method, relating to the selectivity of the method in presence of emtricitabine and efavirenz. They also took copies of Addendum II to the report of the validation of the emtricitabine + efavirenz bioanalytical method, relating to the long-term stability of the analytes in plasma, and to the selectivity of the method in presence of tenofovir. These addenda had not been submitted to the WHO. The raw data supporting these addenda were not reviewed during the inspection, except for the long-term stability of emtricitabine and efavirenz in plasma for 154 days.

In addition during the preparation of the inspection of study No. 124_TENOF_07 the inspectors had recalculated AUC_{0-t} and checked the selection of the C_{max} value for all subjects for both trial periods for tenofovir. They had recalculated the 90 % confidence intervals for these two parameters. During the inspection the inspectors requested tables

of concentrations in Microsoft Excel format for the three analytes of study No. 201_EFAET_08, and used these tables after the inspection to recalculate AUC_{0-t} , check the selection of the C_{max} value, and recalculate the 90 % confidence intervals.

The inspectors discussed with Mr. Tausif Monif, study director for both studies, about the respective responsibilities of the study director and of the test facility management, as defined in GLP, and encouraged Ranbaxy to reconsider which functions he was actually performing.

The documentation relating to the validation of the bioanalytical method used during both studies for the determination of tenofovir in plasma was not reviewed due to time constraints.

A summary of the inspection findings was presented to Ranbaxy as part of the inspection closing meeting.

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, studies No. 124_TENOF_07 (HA423) and 201_EFAET_08 (HA449) were considered to have been conducted at an acceptable level of compliance with WHO GCP and GLP guidelines.

Part 4: References

- Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. WHO Technical Report Series, No. 937, 2006, Annex 7. This document will be referred to in this report as "WHO Guideline";
- Additional guidance for organizations performing in vivo bioequivalence studies. WHO Technical Report Series, No. 937, 2006, Annex 9. This document will be referred to in this report as "WHO Guidance";
- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. WHO Technical Report Series, No. 850, Annex 3, 1995. This document will be referred to in this report as "WHO GCP";
- OECD Principles of good laboratory practice (GLP). [C(97)186/Final], 1997. This document will be referred to in this report as "GLP".

Part 5: Abbreviations

GCP	Good Clinical Practice
GLP	Good Laboratory Practice
LC/MS/MS	Liquid chromatography with tandem mass spectrometry detection
LLOQ	Lower limit of quantification
QC	Quality control (LQC: low quality control, MQC: medium quality control, HQC: high quality control)
SOP	Standard operating procedure
WHO	World Health Organization