

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

Part 1: General information

Name of organization	Matrix Laboratories Limited Clinical Research Centre
Physical address	Saradhi Chambers A-4, Rukminipuri, Near Poulomi Hospital, Main Road, Dr. A.S. Rao Nagar, Hyderabad - 500 062, India
Postal address	Same as above
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Summary of activities	Performance of bioequivalence trials (bioanalytical part only)
Date of inspection	27 and 28 August 2009
Scope of the inspection	Study specific GCP inspection
Programme	Prequalification Programme: Priority Essential Medicines
WHO reference number Study	HA411 Study No. 905/06 Title: A randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of Lopinavir 200 mg + Ritonavir 50 mg tablets of Matrix Laboratories Limited, Hyderabad, India and Kaletra [®] (Lopinavir 200 mg + Ritonavir 50 mg) tablets of Abbott Laboratories, USA, in healthy human adult subjects, under fasting conditions. Clinical phase: 04 January - 01 February 2007 Bioanalytical phase: 14 to 25 April 2007
Investigational product	Lopinavir/Ritonavir 200/50 mg tablets Manufactured by Matrix Laboratories Limited, India Batch number: LORA536001 Date of manufacture: December 2006
Reference product	Kaletra [®] (Lopinavir / Ritonavir) Tablets 200 mg / 50 mg. Manufactured for Abbott Laboratories, North Chicago, IL 60064 USA Lot number: 311069Y40 Expiry date: 01 August 2007
Sponsor	Matrix Laboratories Limited, India

<p>WHO reference number Study</p>	<p>HA467 Study No. 235-08</p> <p>Title: Open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, crossover comparative oral bioavailability study of Ritonavir 100 mg tablets of Matrix Laboratories Limited, India and Norvir[®] (Ritonavir) 100 mg soft gelatine capsules of Abbott Laboratories, North Chicago, IL 60064, USA, in normal, healthy, adult, human subjects under fed condition with a 200 mg dose i.e. 2x100 mg tablets of Test and 200 mg dose i.e. 2x100 mg capsules of Reference products.</p> <p>Clinical phase: 01 to 09 November 2008 Bioanalytical phase: 19 to 29 November 2008.</p>
<p>Investigational product</p>	<p>Ritonavir tablets 100 mg Manufactured by Matrix Laboratories Limited, India Batch number: 1005474 Date of manufacture: June 2008</p>
<p>Reference product</p>	<p>Norvir[®] 100 mg soft gelatine capsule Manufactured for Abbott Laboratories, North Chicago, IL 60064 USA Batch number: 526442E21 Expiry date: 01 September 2009</p>
<p>Sponsor</p>	<p>Matrix Laboratories Limited, India</p>

Part 2: Summary

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

About the company and the facilities of the trial

Matrix started their bioanalytical activities in July 2006, initially at a different location. They moved to the current facility in June 2008. The old facility, where trial No. 905/06 was performed, was not visited during the inspection.

The clinical part of bioequivalence trials was contracted to other CROs (Lotus Labs, Chennai, India for study No. 905/06; GVK Biosciences, Hyderabad, India for study No. 235-08).

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

- 2 LC/MS/MS rooms, equipped with a total of 10 LC/MS/MS systems. Only two of these instruments were available at the time study No. 905/06 was conducted,
- 3 sample processing rooms, including one with low UV light, with the equipment for liquid/liquid and solid phase extraction,
- one balance room,
- one server room,
- one sample storage room, with 5 -70°C deep freezers and 2 -20°C freezers,
- two rooms for the archival of plasma samples, with 3 -70°C deep freezers and 11 -20°C freezers,
- one archive room.

History of inspections (WHO, regulatory authorities etc.)

Matrix had already been inspected 3 times by the WHO since January 2008, including once at the current site.

They were also previously inspected 3 times by the US FDA since September 2007, and once by the Thai FDA in December 2007.

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 primarily focused on specific aspects of study No. 905/06 (as this study had been inspected previously), and of study No. 235/08 (based on questions raised by WHO assessors). (*Note: Findings of the WHO inspection performed on 25 June 2008 relating to study No. 905/06 and already discussed in the report of that inspection are not repeated in this report.*)

On the first day of the inspection, the inspectors introduced themselves. Matrix staff introduced themselves and after exchanging business cards, Matrix staff made a short presentation. The facilities were then visited. During the visit the remaining plasma samples of study No. 905/06 were shown to the inspectors.

The inspectors reviewed briefly the synopsis of the report of study No. 906/06 (fed bioequivalence study on the same investigational products as study No. 905/06), which had not been submitted to the WHO.

On the first day of the inspection, the inspectors checked the documentation and raw data relating to the following activities for study No. 905/06:

- preparation of the calibration and QC samples for the study phase, on 13 April 2007. They recalculated the concentration of the stock and working solutions, and the nominal concentration of the calibration and QC samples. They checked the source of the blank plasma, and the anticoagulant it contained. They checked the number of aliquots frozen;
- "study sample details & processing batch organisation" forms for all analytical runs;
- electronic copies of the chromatograms of subjects No. 03, 07 and 32. For these subjects the inspectors checked the contents of the audit trail and the audit trail settings.

They checked all chromatogram integrations, internal standard response variability, retention times variability, and injection times. They recalculated the concentration of all QC samples in these runs, of all samples in the run of subject No. 03, and of the C_{max} samples of subjects No. 07 and 32. They checked that the nominal concentrations of the calibration samples had been correctly entered into Analyst software. They compared all concentrations in these runs to those reported in the analytical report.

The analytical runs in which the samples of subjects No. 02 and 09 were analysed were accepted for ritonavir, but rejected for lopinavir. The samples of these subjects were therefore re-analysed. As the calibration and QC samples contained both analytes, this resulted in a second, technically valid experimental result for ritonavir. The first value was adequately reported by Matrix. The inspectors asked for a table of comparison of both values for these samples.

On the second day of the inspection, the inspectors:

- reviewed the documentation relating to the determination of the long-term stability of lopinavir and ritonavir in plasma for 173 days. For this run they checked the calculation of the nominal concentration of the fresh calibration and QC samples, reviewed the contents of the audit trail and the audit trail settings, checked all chromatogram

integrations, internal standard response variability, retention times variability, and injection times, and recalculated the concentration of two samples. They checked that the nominal concentrations of the calibration samples had been correctly entered. They compared all concentrations in this run to those reported in the validation report. This review was done using the electronic version of the chromatograms;

- reviewed briefly the synopsis of the report of a fasted bioequivalence study (No. 1578/08) on the same investigational products as study No. 235-08, which had not been submitted to the WHO;

- reviewed the documents relating to the preparation of the calibration and QC samples for study No. 235-08. They recalculated the concentration of the stock and working solutions, and the nominal concentration of the calibration and QC samples. They checked the source of the blank plasma, and the anticoagulant it contained;

- checked that the bioanalytical method used for study No. 235-08 was the same as in the method validation report submitted to the WHO;

- reviewed the documentation relating to the analytical runs for subjects No. 03 and 04 and for subjects No. 11 and 12 in study No. 235-08. For these runs they reviewed the contents of the audit trail and the audit trail settings, checked all chromatogram integrations, internal standard response variability, retention times variability, and injection times, and recalculated the concentration of all QC samples. They checked that the nominal concentrations of the calibration samples had been correctly entered. They compared all concentrations in these runs to those reported in the analytical report. This review was done using the electronic version of the chromatograms;

- reviewed the report of the "incurred sample reanalysis" performed as part of study No. 1578/08.

In addition during the preparation of the inspection of study No. 905/06 the inspectors had checked the calculation of AUC_{0-t} and the selection of the C_{max} value for all subjects for both trial periods for ritonavir. They had recalculated the 90 % confidence intervals for these two parameters.

A summary of the inspection findings was presented to Matrix 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. 905/06 (HA411) and 235-08 (HA467) 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)
WHO	World Health Organization