



Agence française de sécurité sanitaire
des produits de santé

Inspection and companies department

Saint-Denis, on

Clinical trials inspection unit

Person responsible for dossier: O. Le Blaye

Tel: +33.1.55.87.40.19

Fax: +33 1 55 87 40 12

TRANSLATION



INSPECTION REPORT

Response from the inspector to the observations of Mr. Sharma

Title of trial inspected:

An open label, randomized, two way crossover, comparative evaluation of relative bioavailabilities of two formulations of [REDACTED] in healthy adult human subjects under fasting conditions

(Trial no. [REDACTED])

06-11 November 2006

**BA Research
BA Research House
Opp. Pushparaj Towers
Nr. Judges Bungalows
Bodakdev
Ahmedabad - 380 054
India**

Dr Sharma's observations of 16 April 2007 in reply to the inspection report dated 26 December 2006, call for the following response:

- D1 (lack of a contract between the sponsor and BA Research): deviation maintained for the inspected trial; note is taken of the signature, after the end of the trial and before the inspection, of a "Master Services Agreement" between [REDACTED] and BA Research.
- D2 (insufficiencies in the documentation relating to the packaging of investigational medicinal products): deviation maintained for the inspected trial. Modifications of the standard operating procedure and of the standard forms are noted. In order to avoid any risk of confusion and in accordance with Annex 13 to the EU guide to good manufacturing practice, it would be desirable to ensure that the test product and the reference product are not present simultaneously on the work area. In a similar way, packaging articles (including labels) to be used for packaging of the two products should be kept separately and should not be available simultaneously on the work area (line clearance). These points should be specified in the standard operating procedure and should be documented.
- R1 (identity of the investigational medicinal products not mentioned on the labels and not recorded when the products are administered to the subjects): remark maintained for the inspected trial; corrective measures taken after the inspection are noted.
- D3 (anticoagulant used not documented): deviation maintained for the inspected trial; the inspectors had been able to check that at the time of the inspection the anticoagulant used was documented when samples were taken.
- D4 (parameters of the mass spectrometer and weighting factor not specified in the form describing the bioanalytical method): deviation maintained. Parameters actually used for each analytical run can indeed be checked in the document appended to the response to the inspection report, which makes it possible to check that the same, or similar, parameters were used during the trial and during method validation. The availability of this document in the documentation relating to each run had been noticed by the inspectors and is noted in the inspection report. However, as these data can influence the reliability of the data obtained, the weighting factor, and typical values to be used for the mass spectrometer parameters, should be specified in the form which describes the bioanalytical method.
- D5 (mistake in the calculation of the coefficient of variation during pipette control): deviation maintained for the inspected trial; corrective action taken are noted.

The inspectors' observations are not liable to jeopardise the acceptability of the trial data in the context of a marketing authorisation application.

Olivier LE BLAYE

[signed]

Afssaps Inspector





Agence française de sécurité sanitaire
des produits de santé

Inspection and companies department

Saint-Denis, on 25 FEV. 2008

Clinical trials inspection unit

Person responsible for dossier: O. Le Blaye
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Fax: +33 1 55 87 40 12

TRANSLATION



INSPECTION REPORT

Response from the inspector to the observations of Mr. Sharma

Title of trial inspected:

An open label, randomized, two-way crossover, comparative evaluation of relative bioavailabilities of two formulations of [REDACTED] in healthy adult male subjects under fasting conditions

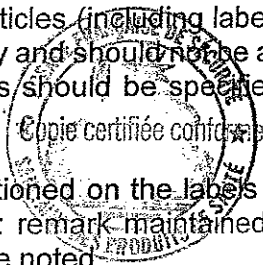
(Trial no. [REDACTED])

06-11 November 2006

BA Research
BA Research House
Opp. Pushparaj Towers
Nr. Judges Bungalows
Bodakdev
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India

Dr Sharma's observations of 16 April 2007 in reply to the inspection report dated 26 December 2006, call for the following response:

- D1 (lack of a contract between the sponsor and BA Research): deviation maintained for the inspected trial; note is taken of the signature, after the end of the trial and before the inspection, of a "Master Services Agreement" between [REDACTED] and BA Research.
- D2 (insufficiencies in the documentation relating to the packaging of investigational medicinal products): deviation maintained for the inspected trial. Modifications of the standard operating procedure and of the standard forms are noted. In order to avoid any risk of confusion and in accordance with Annex 13 to the EU guide to good manufacturing practice, it would be desirable to ensure that the test product and the reference product are not present simultaneously on the work area. In a similar way, packaging articles (including labels) to be used for packaging of the two products should be kept separately and should not be available simultaneously on the work area (line clearance). These points should be specified in the standard operating procedure and should be documented.
- R1 (identity of the investigational medicinal products not mentioned on the labels and not recorded when the products are administered to the subjects): remark maintained for the inspected trial; corrective measures taken after the inspection are noted.
- D3 (anticoagulant used not documented): deviation maintained for the inspected trial; the inspectors had been able to check that, at the time of the inspection, the anticoagulant used was documented when samples were taken.
- D4 (parameters of the mass spectrometer and weighting factor not specified in the form describing the bioanalytical method): deviation maintained. Parameters actually used for each analytical run can indeed be checked in the document appended to the response to the inspection report, which makes it possible to check that the same, or similar, parameters were used during the trial and during method validation. The availability of this document in the documentation relating to each run had been noticed by the inspectors and is noted in the inspection report. However, as these data can influence the reliability of the data obtained, the weighting factor, and typical values to be used for the mass spectrometer parameters, should be specified in the form which describes the bioanalytical method.
- D5 (mistake in the calculation of the coefficient of variation during pipette control): deviation maintained for the inspected trial; corrective actions taken are noted.
- D6 (lack of a printout of the calibration curve parameters, and of the back-calculated concentration of calibration samples, before the exclusion of a calibration sample): deviation maintained for the inspected trial; corrective actions taken after the inspection are noted.
- D7 (error in the documentation relating to the preparation of quality control samples): the mistake is acknowledged by BA Research. The inspectors note that whatever the volume of plasma really spiked (25 or 30 ml), the number of aliquots prepared (41 or 50) would be higher than the number of results reported (18).
- D8 (absence of verification of the specificity of the bioanalytical method used for each analyte vis-à-vis the other analyte): the documentation provided in response to the inspection report shows the lack of any chromatographic interference due to one analyte during the assay of the second analyte. However this demonstration was made using samples which contained only one of the two analytes. In order to totally exclude the possibility of an interference it would have been desirable to extract plasma samples containing a low concentration of the analyte to be determined, and a high concentration of the analyte of which the lack of interference was to be



demonstrated, in order to verify the lack of any influence on the concentration measured. However, the risk of an interference during sample extraction or during ionisation is very low. The response can be considered as satisfactory.

- D9 (non-justified exclusion of a quality control sample during the validation of a bioanalytical method: deviation maintained for the inspected trial; corrective actions taken after the inspection are noted.

The inspectors' observations are not liable to jeopardise the acceptability of the trial data in the context of a marketing authorisation application.

Olivier LE BLAYE

[signed]

Afssaps Inspector



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER

C.T. Viswanathan, Ph.D.
Associate Director (Bioequivalence), Chief, GLP and Bioequivalence Branch
Division of Scientific Investigations, CDER, Food and Drug Administration
7520 Standish Place, MPN 1, Rockville, MD 20855. U.S.A

DATE(S) OF INSPECTION

September 20-21, 2007

FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Naveen Sharma, Sr. Vice President - Operations

FIRM NAME

BA Research India Limited

STREET ADDRESS

Opposite Pushparaj Towers, Nr. Judges Bungalows

CITY, STATE AND ZIP CODE

Bodakdev, Ahmedabad 380 054. India

TYPE OF ESTABLISHMENT INSPECTED

Clinical and Bioanalytical Facility

DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

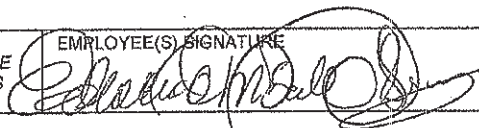
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

Observations from Study [REDACTED]

1. Failure to seek consent under circumstances that provide that the prospective subject or the subject's representative sufficient opportunity to consider whether or not to participate and minimize the possibility for coercion or undue influence.
2. Failure to justify abnormal laboratory values in case report forms.
3. Removal and return of subject plasma samples and quality control samples from the freezer during analysis were not documented in the freezer log.

SEE
REVERSE
OF THIS
PAGE

EMPLOYEE(S) SIGNATURE



EMPLOYEE(S) NAME AND TITLE (Print or Type)

Edward McDonald
Sriram Subramaniam, Ph.D.

DATE ISSUED

September 21, 2007

The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."