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WARNING LETTER

Food and Drug Administration
Rockville MD 20857

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

Reference No. 48-00-1001

[] M.D.
Clinical Pharmacology Associates
2060 N.W. 22nd Avenue
Miami, FL 33142

OCT 18 1999

Dear Dr. []

During February and March of 1999, investigators from the Food and Drug Administration's (FDA) Florida District Office and staff from the Division of Scientific Investigations inspected the following bioavailability studies in which you participated as the investigator of record:

IND [] Study []
IND [] Study []
IND [] Study []

This inspection was conducted as part of the FDA's Bioresearch Monitoring Program which is designed, in part, to monitor the conduct of research involving investigational drug products and to assure that the rights and welfare of subjects participating in such studies have been protected.

We have evaluated the report of this inspection, and your March 9, 1999 response to the FDA Form 483 observations issued to you at the conclusion of the inspection. Your response fails to adequately address your personal responsibility, conduct, and corrective actions, as the investigator of record, for the violations listed below. The applicable provisions of the Code of Federal Regulations (CFR) are cited for each violation.

- 1. Failure to protect the rights, safety, and welfare of the subjects in that you did not assure that effective means of contraception were employed [21 CFR 312.60].

Contrary to your response, the screening process did not sufficiently address the type and usage of effective birth control procedures employed by the subjects in Study

[] Additionally, the continued usage of effective contraceptive methods was not monitored during the study. This is evident from the fact that two subjects became pregnant during the study. One of the pregnant subjects admitted to not using an effective contraceptive method. In your response letter, you provided an amended screening questionnaire to verify the type and usage of contraceptive methods by the subjects. However, your response does not address how you will monitor the continued usage of effective contraceptive methods *during* such studies.

Furthermore, the protocol required investigation of the outcome of pregnancies and any postnatal sequelae in the infants. However, you did not investigate the outcome of the pregnancies for the two subjects until the FDA investigators requested the information. It is important that such follow-up investigations be conducted promptly to assure the safety and welfare of subjects.

2. Failure to provide consent information to non English-speaking subjects in a language understandable to the subjects in Studies [] and [] [21 CFR 50.20].

During the inspection, your staff stated that it is the clinic's policy not to issue English consent forms to subjects who do not understand English. In contrast, our investigation found that English consent forms were issued to Spanish-speaking subjects who did not understand English. Consent forms must be in a language understandable to the subjects.

3. Failure to maintain adequate records of the disposition of the drug, including dates, quantity and use by the subjects in Studies [] and [] [21 CFR 312.62(a)].

In your response, you provided a copy of the proposed drug inventory form for future studies. However, your response fails to address the practices associated with the implementation of this form. For example, issues such as who will be responsible for dispensing study medication and the mechanism to assure the accuracy of the drug dispensed/remaining are not addressed.

4. Failure to follow the randomization schedules specified in the protocol [21 CFR 312.60].

Your source documents revealed that you failed to assure dosing according to the randomization code in Study []. Your explanation that the inconsistencies are recording errors is not satisfactory as: 1) the errors were identified five months after dosing and 2) the drug inventory record at the time of Study [] was a retrospective record. Recording errors, should be promptly identified and corrected. Corrections should include the reason for the changes, the responsible person and the date.

Also, you should be aware that the clinic's current practice of allowing subjects to help in the kitchen is not acceptable for bioavailability/bioequivalence studies wherein subjects receive controlled diets.

The above description of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations. Failure to immediately correct these violations may result in regulatory action without further notice.

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You should notify this office in writing, within fifteen (15) working days of receipt of this letter, with specific steps you have taken to correct these violations.

If you have any questions, please contact:

C.T. Viswanathan, Ph.D.
Associate Director, Bioequivalence
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 151
Rockville, Maryland 20855
Telephone: (301) 827-5460

Sincerely,

A handwritten signature in black ink, appearing to read "David A. Lepay". The signature is fluid and cursive, written over a white background.

David A. Lepay, M.D., Ph.D.
Director
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research