DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

JUL 27 1999

WARNING LETTER

Food and Drug Administration
Rockville MD 20857

Certified Mail
Return Receipt Requested

Reference No: 99-HFD-340-0701

James K. Leslie
President and Chief Executive Officer
PharmaKinetics Laboratories, Inc.
302 West Fayette Street
Baltimore, MD 21201

Dear Mr. Leslie:

Your facility was inspected on four occasions between May 5, 1998 and June 18, 1999, by investigators from FDA's Baltimore District Office and staff from the Division of Scientific Investigations to review your firm's activities related to the conduct of bioequivalence studies. These inspections are a part of FDA's Bioresearch Monitoring Program which is designed, in part, to validate the clinical and analytical portions of bioequivalence studies and to assure that the rights and welfare of subjects participating in such studies have been protected. The inspections covered studies for the following applications:

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We have evaluated the reports of these inspections and your responses to the FDA Form 483 observations and conclude that your firm has failed to conduct these bioequivalence studies in accordance with the protocol, in areas set forth to protect the rights, safety and welfare of the subjects, and with respect to inclusion/exclusion criteria. We must emphasize that matters of failing to follow the protocol were previously cited in the December 20, 1993 Warning Letter issued to your facility.

Specifically, you failed to fulfill your responsibility in assuring that all protocol requirements were met in the following examples:

1. ANDA[ ] Clinical investigators were not present for all periods of subject dosing although their presence was a protocol requirement, and

   ANDA[ ] Clinical investigators failed to remain on-site in all periods for the entire post-dosing duration specified by the protocol.

In your December 11, 1998 response to the FDA Form 483 observations, you state that "dosing will not occur if the protocol requires the presence of a physician and the physician is not on-site." However, your response failed to address the mechanism by which the presence of the clinical investigator will be assured.

2. ANDA[ ] Urine screens for pregnancy at check-in were not verified as negative prior to dosing in both study periods.

In your January 14, 1999 response to the FDA Form 483 observation, you agreed that there was no documentation to indicate that the laboratory reports were reviewed by the clinical investigator prior to dosing.

3. ANDA[ ]Six subjects enrolled in two[ ]studies failed to meet protocol inclusion/exclusion criteria including weight requirements, over-the-counter drug product use and marijuana use.

In your December 11, 1998 response, you agreed with these observations. However, your response failed to address how violations of protocol inclusion/exclusion criteria will be prevented in future studies.

4. You failed to assess all available medical history data to assure that subjects met the protocol inclusion/exclusion criteria and that contradictory information had been resolved. For example:

   a. ANDA[ ]A subject rejected from a different study for high amylase levels was included in the[ ]study even though his amylase level was not rechecked. You agreed in your July 28, 1998 response to the FDA Form 483 observation that appropriate follow-up for this subject was not completed.

   b. ANDA[ ] Smoking histories given by four subjects at screening were not verified as accurate and contradicted information in their medical charts. These subjects would not have met the entry criteria if screening personnel had considered the earlier responses of these subjects.

Furthermore, your firm failed to: (a) document that subjects in the[ ]and[ ] studies met the protocol requirements regarding caffeine abstention prior to period 2 dosing; (b) inform 77 subjects in a[ ]study that the informed consent form they had already signed contained an error; (c) administer the revised informed consent form approved by the IRB to 5 subjects in the same[ ]study; and (d) evaluate electrocardiograms required by the [ ]protocol according to your standard operating procedure. The exact studies and patient identification numbers involving such violations were cited on the various FDA Forms 483 issued to you (copies enclosed).

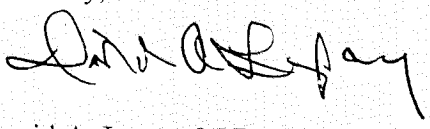
The above discussion of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is unacceptable that practices at your facility have not improved since the December 20, 1993 Warning Letter. Failure to immediately correct these violations may result in regulatory action without further notice.

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

If you have any questions concerning these matters, 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, MD 20855
Telephone: (301) 827-5460

Sincerely,



David A. Lepay, M.D., Ph.D.
Director
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