DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Warning Letter

Certified Mail-Restricted Delivery
Return Receipt Requested

Ref# 99-HFD-340-0403

MAY 19 1999

Bruce Ettinger, M.D.
4141 Geary Boulevard
San Francisco, California 94118

Dear Dr. Ettinger:

Between December 9, 1998 and January 6, 1999, Dr. Gerald N. McGirl, representing the Food and Drug Administration (FDA), conducted an inspection of your conduct, as investigator of record, of the following clinical study: Protocol [ ] sponsored by [ ]

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

We have evaluated the inspection report, the documents collected during the inspection, and the three-page Inspectional Observations (Form FDA 483) provided to you at the conclusion of the inspection. We find that you significantly violated the Federal Food, Drug, and Cosmetic Act and FDA regulations governing the study of investigational new drugs and the protection of human research subjects in the following respects:

VIOLATIONS RELATED TO RECORD KEEPING AND RECORD RETENTION [21 CFR 312.62].

1. You failed to maintain x-rays to verify the presence of kidney stones for 8 of 13 subjects reviewed. The prevention of stone recurrence, that is the efficacy of the test article, was determined by abdominal x-ray.

VIOLATIONS RELATED TO IRB APPROVAL
[21 CFR 312.60, 312.53(c)(1)(vi)(d)and 312.53(c)(1)(vii)].

1. You failed to maintain documentation to show continuing IRB approval of the protocol for the time periods 8/22/91 to 12/17/92, and 12/21/93 to 3/15/94. For 13 subjects, records show that all were enrolled in the study between 8/22/91 and

12/17/93. In addition, the annual report to the IRB dated 10/27/92 states that 61 subjects were enrolled in the study between October 1991 and October 1992.

2. You failed to maintain documentation to show IRB approval of the 12/1/91 version of the consent form which was issued to subjects 02-006, 02-008, 02-010, 02-108, 02-114, 02-121, 02-132, and 02-141.

VIOLATIONS RELATED TO THE INFORMED CONSENT FORM
[21 CFR 312.60 and 21 CFR 50].

1. You failed to utilize the most current consent form dated 12/1/91. We note that subjects 02-015, 02-019, 02-101, 02-102 and 02-106 signed the consent form, approved 8/1/90, on 5/5/92, 7/13/92, 2/10/94, 12/10/91, and 12/3/93, respectively.

2. Your study records contained two consent forms dated 8/1/90. Subjects 02-015 and 02-019 signed a different version of an 8/1/90 consent form than subjects 02-101, 02-102 and 02-106. In addition, it is not clear which version of the consent form was approved by the IRB on 8/21/90.

3. The consent forms used in this study did not include a statement regarding whom the subject should contact in the event of a research-related injury.

PROTOCOL VIOLATIONS [21 CFR 312.60]

1. The protocol required that stool samples for occult blood would be checked four months after treatment and at the first visit of each year thereafter. You did not perform this test for any subject enrolled in the study.

2. The protocol states that any documentation of new stone formation, which includes passage of a stone with no reduction in the number of preexisting stones, will mandate withdrawal from the study. Subject 02-141 entered the study on 10/13/92. Study records document that a stone was passed on 9/24/93, with no reduction in the number of stones otherwise recorded. This subject should have been withdrawn; however, study medication was dispensed on 11/9/93.

The above description of our findings is not intended to be an all-inclusive list of your violations and deficiencies. Please provide this office, within 15 working days of your receipt of this letter, a written response of the corrective actions you have taken or plan to take to prevent similar violations in the

future. Failure to adequately and promptly correct these matters may result in further regulatory action.

We appreciate the cooperation shown Investigator McGirl during the inspection.

If you have any questions, please contact Dr. Antoine El-Hage at (301) 594-1032, FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II/HFD-344
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, Maryland 20855

Sincerely yours,

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