DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Herman Zaharowitz, M.D.
4957 38th Avenue North, Suite C
St. Petersburg, Florida 33710-8502

Ref: 06-HFD-45-0803

Dear Dr. Zaharowitz:

Between October 19 and December 1, 2004, Mr. Paul Figarole, representing the Food and Drug Administration (FDA), conducted an investigation of alleged non-compliance with regulations and met with you to review your conduct of the following clinical investigation:

Protocol[ ]entitled "A Phase III, Randomized, Multicenter Study Comparing the Safety and Efficacy of Oral[ ]versus Allopurinol in Subjects with Gout" of the investigational drug[ ]performed for[ ]

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety and welfare of the human subjects of those studies have been protected. From our review of the establishment inspection report, the documents submitted with that report, and your written response dated December 15, 2004, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Figarole presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. **You failed to protect the rights, safety, and welfare of subjects under your care [21 CFR 312.60].**

   a. Subject #2223 presented for the Week 52 study visit on August 14, 2003 with a complaint of "indigestion." For this visit, the protocol required, among other things, that the subject receive a complete physical exam and that an ECG be performed. The subject did not receive a physical exam and was not evaluated by you at this visit. He was seen only by the study coordinators,[ ]R.N., and[ ]L.P.N. An electrocardiogram was performed, but it was not reviewed by you or the study coordinators on that date. This electrocardiogram

showed S-T changes with a machine reading of "probable myocardial infarction." According to the sponsor's monitoring report dated August 21, 2003, the subject went to the Emergency Room on August 17, 2003, was diagnosed with a myocardial infarction, and had an angioplasty. Also according to this report, Mr.[ ]told the monitor that "Dr. Zaharowitz has not reviewed this EKG result as of today and is not aware of the EKG report findings." Mr.[ ]also confirmed that neither he nor Mr.[ ]had read the results of the EKG because "there was no need to since Dr. Zaharowitz was not present." Your failure to adequately supervise those qualified and authorized to perform these tasks or to personally evaluate this subject's complaint of indigestion, including failure to review the electrocardiogram to determine whether this symptom may be of cardiac origin, failed to protect the rights, safety, and welfare of this subject.

b. Laboratory results were not reviewed in a timely fashion. In some cases you did not review results for several weeks. The protocol states that they must be reviewed and assessed for significance by the investigator or sub investigator. For example:

- Subject #2190 had laboratory tests done July 11, 2003, but the report was not signed by you until August 7, 2003.
- Subject #2177 had laboratory tests done on July 11, 2003 but the report was not signed by you until August 14, 2003
- Subject #2223 had laboratory tests done on August 4, 2003, but the report was not signed by you until September 4, 2003
- Subject #2224 had laboratory tests done on August 5, 2003, but the report was not signed by you until September 4, 2003

By not reviewing laboratory tests results in a timely manner, you could have missed clinically important developments in study subjects, thereby you failed to protect the rights, safety and welfare of study subjects.

2. You failed to conduct the clinical investigation according to the investigational plan [21 CFR 312.60].

According to the "Site Personnel Team List/Authorized Signature List", only the principal investigator and sub-investigators (all physicians) were authorized to perform physical examinations for protocol[ ]In addition, no other individuals listed were qualified to perform physical examinations without oversight by a physician. However, the following subjects had physical exams performed by [ ](L.P.N.):

- Subject #2177 on July 11, 2003 and August 6, 2003
- Subject #2190 on July 10, 2003
- Subject #2192 on August 4, 2003

- Subject #2224 on August 5, 2003
- Subject #2225 on July 7, 2003

In your Memo To File dated October 7, 2003, you stated that "there has been no communication, information or request to participate or do physical exams [by the contract research organization]." The absence of specific direction from the contract research organization does not excuse you from your obligations as clinical investigator for the study site. As clinical investigator, you should have been aware of the requirements of the protocol, including the need for complete physical examinations at specified study visits.

3. **You failed to obtain the legally effective informed consent before involving a subject in research [21 CFR 50.20, 21 CFR 50.27, and 21 CFR 312.60].**

When you signed the Form FDA 1572 on July 1, 2003, you agreed to ensure that the requirements relating to informed consent were met. The IRB approved a revised Informed Consent Document (ICD) on July 9, 2003 (to incorporate a protocol amendment). The previous version of the ICD specified that the form expired on July 22, 2003. Subjects #2190 and 2192 signed the outdated version of the ICD on August 7, 2003, subject #2223 signed the outdated version on August 4, 2003, and subject #2224 signed the outdated version on August 5, 2003.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs. It is your responsibility as the investigator of record to ensure adherence to FDA regulations. You must address these deficiencies and establish procedures to ensure that any on-going or future studies will be in compliance with the regulations.

Because of the departures from FDA regulations discussed above, please inform this office, in writing, within 15 working days of your receipt of this letter, of the actions you have taken or plan to take to prevent similar violations in the future. Failure to adequately and promptly explain the violations noted above may result in further regulatory action.

If you have any questions, please contact Leslie Ball, M.D., at (301) 594-1032; FAX (301) 827-5290. Your written response and any pertinent documentation should be addressed to:

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Sincerely yours,

{See appended electronic signature page}

Joseph P. Salewski
Director (Acting)
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Joseph Salewski
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