DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Robert J. Amato, D.O.
6560 Fannin Street
Suite 2050
Houston, TX 77030

Ref. No. 07-HFD-45-0801

Dear Dr. Amato:

Between August 1 and 5, 2005, Robert T. Lorenz, representing the Food and Drug Administration (FDA), conducted an investigation and met with you, to review your conduct of the following clinical investigations:

Protocol [ ] "Phase II Study of [ ] Treatment of Patients with Metastatic Renal Cell Carcinoma," performed for [ ]

Protocol [ ] "A Phase II Open-Label Study of the Safety and Efficacy of [ ] in subjects with Metastatic Hormone-Refractory Prostate Cancer (HRPC)," performed for [ ]

Protocol [ ] "A Phase 2 Randomized Study Evaluating the Safety and Efficacy of [ ] in Subjects with Advanced Renal Cell Carcinoma," performed for [ ] and

Protocol [ ] "Phase II Trial of [ ] for Treatment of Metastatic Renal Cell Carcinoma," performed for [ ]

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate 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 and the documents submitted with that report and your August 17, 2005 letter written in response to the Form FDA 483, Inspectional Observations, 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. Lorenz presented and discussed with you Form FDA 483,

Inspectional Observations. The following violations from Statute and IND regulations 21 CFR 312 are noted:

1. **You failed to ensure that an Institutional Review Board (IRB) was responsible for the initial and continuing review and approval of above-referenced clinical investigations [21 CFR 312.66].**

Specifically, you conducted the above-referenced clinical investigations at Baylor College of Medicine from approximately March 2002 until December 2004, when you moved to The Methodist Hospital Research Institute (TMH). The Baylor College of Medicine (BCM) Institutional Review Board (IRB) met December 7, 2004 to review several matters related to its continuing oversight of research for which you served as principal investigator. In a letter to you dated December 14, 2004 the BCM IRB noted it had been in communication with you regarding findings of non-compliance since July 2002, without completion of all required corrective actions. As such, the BCM IRB stated that, at its December 7, 2004, meeting, it had reached the following decisions: 1) immediate suspension of all BCM research activity for which you serve as principal investigator; 2) requirement that you remove yourself from all BCM human subject research activities; and 3) suspension from seeking BCM IRB review and approval of human subject research activities for a period of four years. The BCM IRB stated that you should contact the BCM Department of Urology for instructions regarding the clinical care of current research subjects.

Our investigation found that in October 2004, you began transferring oversight of your clinical research from Baylor IRB to the[ ]IRB in [ ]The BCM IRB continuing review and approval of your protocols officially terminated on December 7, 2004. Our investigation found the following:

a. [ ]Protocol[ ]"Phase II Study of[ ]Treatment of Patients with Metastatic Renal Cell Carcinoma." Our records show that the BCM IRB initially approved this study for the period October 5, 2004 to April 5, 2005. You applied for initial[ ]review of the protocol on 01/04/2005. A lapse of IRB approval occurred between December 7, 2004 (date of suspension by BCM IRB) until February 22, 2005[ ]IRB approval), approximately 2.5 months;

b. [ ]Protocol[ ]"A Phase II Open-Label Study of the Safety and Efficacy of[ ]in Subjects with Metastatic Hormone-Refractory Prostate Cancer." Our records show that BCM IRB approved this study from March 2, 2004 to March 2, 2005; you applied to[ ]IRB for initial review on December 23, 2004. A lapse of IRB approval occurred between December 7, 2004 (date of suspension by BCM IRB) until February 22, 2005 [ ]IRB approval), approximately 2.5 months;

c. [ ]Protocol[ ]"A Phase 2 Randomized Study Evaluating the Safety and Efficacy of[ ]in Subjects with Advanced Renal Cell Carcinoma." Our records show you applied for initial[ ]IRB review on October 16, 2004; your BCM IRB approval lapsed on December 7, 2004 (date of suspension by BCM IRB)

and you did not receive[ ]IRB approval until February 22, 2005, an approximate 2.5 month lapse;

d. [ ]Protocol[ ]"Phase II Trial of [ ]for Treatment of Metastatic Renal Cell Carcinoma." Our records show that you requested initial[ ]IRB approval on October 6, 2004. The BCM IRB approval ended on November 4, 2004; you did not receive[ ]IRB approval until November 23, 2004, an approximate 3 week lapse.

The[ ]IRB did not grant approval for protocols [ ] until February 22, 2005. Our investigation found that you continued to treat subjects under all 3 protocols, even though the IRB approval had lapsed. In your February 15, 2005, letters to the[ ]IRB regarding these three studies and in your August 17, 2005 response to Form FDA 483, you state the reason you continued study procedures for study participants was for their safety and welfare, and because drug was controlling their disease. Although we acknowledge your concern for the safety and welfare of the study participants, we also note that the BCM IRB specifically instructed you, in its December 14, 2004 letter notifying you of its decision to suspend you from human subject research activities at BCM, to contact the BCM Department of Urology for instructions regarding the clinical care of current research subjects. Your explanation is inadequate. It is the clinical investigator's responsibility to ensure continuing review and approval by an IRB.

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

Specifically, Protocol[ ]required that doses of the investigational agent be administered on specific days for each cycle, and that the clinical investigator must explain in the case report forms (CRFs) if the entire dose is not given, interrupted, or given off schedule. Our investigation found that for Subject #006[ ]you did not administer doses of investigational agent on days 15 through 19 for Cycle 7, on days 15 through 19 for Cycle 8, or on days 15 and 19 for Cycle 9. Furthermore, you did not provide an explanation for these lapses in dosing on the CRF.

We note that, in your August 17, 2005 letter to FDA you include a Memoradum from Dr.[ ]dated August 4, 2005 and initialed by you on August 18, 2005. This Memorandum reports a "change in treatment for patients on Protocol[ ]and states that "[p]atients . . . who have excess toxicity in the clinical judgment of the investigator may skip their B Treatment week." However, this memorandum was written more than 8 months after Subject #006[ ]should have received Cycles 7, 8, and 9, and you provided no evidence that this change of protocol was submitted to and approved by your IRB. In addition, your August 17, 2005 letter to FDA does not explain what responsibility Dr.[ ]had for the study.

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

Specifically, our investigation found that for Protocol [ ] you did not record drug lot numbers on the CRF for Subject 023 [ ] who received the investigational drug [ ] 20 times over two cycles. We note that in your August 17, 2005 letter to FDA you include a CRF for Subject 023 [ ] signed by you on August 18, 2005. This CRF states '804060f' as the lot number for all doses of the investigational drug received by Subject 023 [ ] However, providing a complete CRF more than 8 months after a subject receives the investigational drug is not sufficient to meet your obligations under the regulations. We acknowledge that in your August 17, 2005 letter to FDA, you discuss several corrective actions you have implemented to ensure that case histories for all future IND studies will be properly documented. You state that you have hired two experienced Clinical Trial Managers, a Regulatory Compliance Manager, and several research assistants, to provide supervision and quality management of all the clinical trials conducted under your supervision in the [ ] Oncology Program. In addition, you state that you plan to implement what you refer to as a Quality Management Plan to assess the quality of the operational procedures and recording of the research data. We trust these measures will help ensure that any on-going or future studies will be in compliance with FDA regulations.

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

Within fifteen (15) days of receipt of this letter, you should notify this office in writing of the actions you have taken or will be taking to prevent similar violations in the future. Include any documentation necessary to show that corrections have been achieved. Failure to adequately and promptly explain the violations noted above may result in regulatory action without further notice.

If you have questions, please contact Joe Salewski at (240) 276-8821, FAX (240) 276-8811. Your written response and any pertinent documentation should be addressed to:

Joe Salewski
Acting-Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
7520 Standish Place,
Rockville, Maryland 20855

Sincerely yours,

Joe Salewski
Acting-Director
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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