DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Reference No. 06-HFD-45-0601

John Mendelsohn, M.D., President
MD Anderson Cancer Center
1515 Holcombe Blvd
Houston, Texas 77030-4009

Dear Dr. Mendelsohn:

Between October 19 and November 2, 2004, Mr. Joel Martinez, Mr. Patrick Stone, and Ms. Mary Mease, representing the Food and Drug Administration (FDA), inspected the MD Anderson Cancer Center Institutional Review Board (IRB). The purpose of this inspection was to determine whether the IRB was in compliance with the regulations governing IRBs and those governing the protection of human subjects participating in clinical trials contained in Title 21 of the Code of Federal Regulations (CFR), Parts 50 and 56. These regulations apply to clinical studies for products regulated by FDA.

In addition, between October 18 and October 22, 2004, Mr. Richard Fejka and Mr. Patrick Stone from FDA inspected the M.D. Anderson Radioactive Drug Research Committee (RDRC) and met with the RDRC's then-Chair, [ ] M.D. That inspection was conducted to assess the RDRC's compliance with 21 CFR Part 361, including whether the RDRC's approval of the following clinical study met the regulatory requirements: Protocol [ ] entitled "Biodistribution and Pharmacokinetics of [ ] in Patients with Breast Cancer." This study involved the use of the investigational drug [ ].

As a result of this RDRC inspection, FDA concluded that the RDRC did not adhere to the applicable statutory requirements and regulations governing the operation of RDRCs and the protection of human subjects in 21 CFR Parts 361, 50, and 56. Dr. John Jenkins from FDA's Center for Drug Evaluation and Research (CDER) issued a letter dated December 8, 2004, to Dr. [ ] withdrawing approval of the RDRC in accordance with 21 CFR 361.1(c)(4) (copy attached). That letter contained a list of the regulatory deficiencies that were also noted at the inspection. We remind you that if M.D. Anderson wishes to establish an RDRC in the future, that a new application must be submitted for FDA approval. In addition, as Dr. Jenkins stated in his letter, if applying to reestablish the

RDRC, you must cite the corrective actions the institution has implemented to avoid the deficiencies listed in the letter.

With regard to the IRB inspection, from our evaluation of the establishment inspection report, the documents submitted with that report, and your December 7, 2004 and August 14, 2005, written responses to the Form FDA 483, we conclude that the IRB failed to adhere to 21 CFR Parts 50 and 56 and, therefore, failed to protect the rights and welfare of study subjects. We are aware that at the conclusion of the inspection, our investigator, Mr. Stone, presented and discussed with [ ] M.D., Ph.D., IRB Chairman, a Form FDA 483, Inspectional Observations.

The regulatory violations were based on the review of IRB procedures for the following studies:

Protocol [ ] for Imaging of Apoptosis in Primary Breast Cancer (PBC)-A Pilot Study"

Protocol [ ] "A Randomized Phase II Study of [ ] + [ ] versus [ ] Alone as Maintenance Therapy for Multiple Myeloma Following Autologous Bone Marrow Transplantation"

Protocol [ ] "An Open Label, Single Arm, Multi-Center, Safety, Pharmacokinetic and Pharmacodynamic, Phase II Study of [ ] in Pediatric and Adult Subjects with Thrombocythemia Secondary to Myeloproliferative Disorders"

Protocol [ ] "A Phase II Trial of [ ] plus [ ] in Patients with Advanced Renal Cell Cancer Previously Treated with Immunotherapy"

We wish to emphasize the following:

1. **The IRB failed to assure that the risks to subjects were minimized by use of study procedures that are consistent with sound research design and that do not unnecessarily expose human subjects to risks [21 CFR 56.111(a)(1)].**

   Our investigation found that the [ ] protein used to prepare the investigational drug [ ] used in Protocol [ ] was derived from human placenta and was labeled "not for drug, household or other uses." The Material Safety Datasheet (MSDS) for [ ] stated, "Biohazard... Handle as if capable of transmitting infectious agents." Also, because the [ ] was intended for intravenous administration, it should have been prepared under conditions that would assure that it was sterile and pyrogen-free. Also, because the [ ] is a protein from a human source, it has the potential to cause untoward immunogenic reactions. Written IRB records and audiotapes of the IRB meetings at which the IRB considered Protocol [ ] contain no discussion of the potential for transmissible pathogens with the [ ] component, the risk of non-sterility

and pyrogenicity of [ ] or the immunogenic potential of the [ ] component. By failing to consider these risks, the IRB failed to assure that risks to subjects were minimized.

In its December 7, 2004 written response, the IRB acknowledged that the study was "incorrectly" approved and maintained that new procedures have been implemented to ensure that a protocol will not be approved until all relevant issues are considered.

In the IRB's August 8, 2005 follow-up written response, the IRB indicated that all subjects had been notified of potential risks of transmissible pathogens with [ ] and tested to determine whether they had been exposed to infectious agents. The response also indicated that testing was performed on four vials of the lot of [ ] that was used in the preparation of the drug product. The IRB reported that results of the testing of study subjects and lots used in preparation of the drug product (testing for an array of viruses that could potentially be present in a product derived from human sources) indicated that the subjects enrolled in protocol [ ] were "unlikely" to have been exposed to infectious agents as a result of their participation in the study.

2. **The IRB failed to approve pediatric research in compliance with the requirements of 21 CFR Part 50, Subpart D [21 CFR 56.111(c)].**

To approve research in which some or all of the subjects are children, an IRB must also determine that the research complies with the requirements of 21 CFR part 50, subpart D (Additional Safeguards for Children in Clinical Investigations). For protocol [ ] our investigation found no evidence that the IRB made the appropriate findings required by 21 CFR 50, Subpart D. In its December 7, 2004 written response, the IRB acknowledged this deficiency and stated that it will document the vote and discussion regarding risks and benefits associated with pediatric studies, as required by 21 CFR Part 50, subpart D.

3. **The IRB failed to require that informed consent was obtained from study subjects in accordance with and to the extent required by 21 CFR part 50 [21 CFR 56.111(a)(4)].**

   a. The IRB-approved informed consent document (ICD) did not contain all of the required elements of informed consent. [21 CFR 50.25(a)]

      i. The ICD did not contain a description of "any reasonably foreseeable risks or discomforts" as required by 21 CFR 50.25(a)(2). The ICD identified skin rash as the only reasonably foreseeable risk or discomfort associated with participation in the study. As discussed in item #1, the reasonably foreseeable risks and discomforts associated with receiving [ ] also included the possibility of infectious disease due to potential exposure to transmissible pathogens, immunologic reactions due to exposure to a

protein derived from a human source, and exposure to a non-sterile drug substance. The subjects were also not informed of the risks associated with receiving intravenous technetium (Tc), a radioactive substance, or the radiation exposure associated with whole body imaging. In its December 7, 2004 written response, the IRB stated that it had implemented procedures to inform subjects and that the consent document was revised to include important risk information, which was provided to the subjects.

ii. The ICD did not include a statement that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled as required by 21 CFR 50.25(a)(8).

b. The IRB failed to assure that informed consent to participate was obtained under circumstances that minimized the possibility of coercion or undue influence. [21 CFR 50.20]

The ICD stated that[ ]has been authorized by the FDA for use in research only." This statement is not accurate in that FDA did not authorize the use of[ ]for research purposes. In fact, FDA was not aware that this study was being conducted and therefore could not have authorized use of[ ] in this clinical investigation. Inclusion of this statement in the ICD may have given subjects a false sense of security regarding the safety of the research and unduly influenced their decisions to participate in the study. In its December 7, 2004 written response, the IRB acknowledged that the statement was not accurate and have since deleted the statement from the ICD.

4. The IRB's written procedures for initial review do not adequately reflect the regulatory requirements for obtaining informed consent [21 CFR 56.108(a)(1)].

The IRB's written procedures allow for the English version of IRB-approved ICDs to be orally translated for non-English speaking subjects. Records indicate that the IRB approved ICDs for protocols[ ]that provided for oral translations of the English versions of the ICDs. For studies that enroll non-English speaking subjects, oral translation of an IRB-approved ICD is not adequate to satisfy the requirement for obtaining and documenting informed consent. To meet the requirements of 21 CFR 50.20 and 50.27, the ICD must be in language understandable to the subject or the subject's representative. While 21 CFR 50.27(b)(1) does allow for the written consent document to be read to the subject, it does not allow for it to be "read" in a different language, and the regulation requires that the subject be given adequate opportunity to read the ICD before it is signed. In this case, a non-English speaking subject would not be able to read the ICD.

This letter is not intended to be an all-inclusive list of deficiencies for the protocols reviewed and approved by the IRB.

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. We acknowledge your written responses to items #1, #2, #3a.i. and #3b. Failure to adequately and promptly explain violations noted above under #3a.ii. and #4 may result in further regulatory action.

If you have any questions, please contact Dr. Leslie Ball, 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 Salewski
Director (Acting)
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND [ ]	[ ]	[ ]

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/s/

JOSEPH SALEWSKI
06/15/2006