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-45-0602

Massimo Cristofanilli, M.D.
MD Anderson Cancer Center
1515 Holcombe Boulevard, Box 424
Houston, Texas 77030

Dear Dr. Cristofanilli:

Between October 18 and November 3, 2004, Mr. Joel Martinez, Mr. Patrick Stone, Ms. Mary Mease, Mr. Richard Fejka, and Dr. Mathew Thomas, representing the United States (U.S.) Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (Protocol [ ] entitled "Biodistribution and Pharmacokinetics of [ ] in Patients with Breast Cancer") of the investigational new drug [ ] for which you served as the clinical investigator. The purpose of this inspection was to determine whether your conduct as a clinical investigator was in compliance with the regulations governing clinical investigations and those governing the protection of human subjects participating in clinical trials contained in Title 21 of the Code of Federal Regulations (CFR), Parts 312, 50 and 56. These regulations apply to clinical studies for products regulated by FDA. At the conclusion of the inspection, Mr. Patrick Stone presented and discussed with you the items listed on Form FDA 483, Inspection Observations.

From our review of the establishment inspection report, the documents submitted with the report, your January 5, 2005 written response to Form FDA 483, and other pertinent information obtained by the Agency, 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 wish to emphasize the following:

1. **You administered an investigational new drug to human subjects without an effective investigational new drug (IND) application [21 CFR 312.2(a); 21 CFR 312.40(d)].**

   FDA regulations require that an investigator not administer an investigational drug in a clinical investigation until there is an IND in effect [21 CFR 312.40(d)].

   Our investigation determined that you were the investigator for this study and that you administered [ ] to study subjects without an IND in effect. During the inspection and in your written response of January 5, 2005, you acknowledged enrolling subjects into protocol [ ] and administering the investigational new drug [ ] without an IND in effect. In your written response you acknowledged that this study should have been conducted under an IND and stated that this was an error based on your misinterpretation of FDA's regulatory requirements.

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

   As investigator, you are responsible for protecting the rights, safety, and welfare of subjects under your care [21 CFR 312.60].

   Our investigation determined that you administered an investigational new drug, [ ] to human subjects enrolled in protocol [ ] without ensuring that the investigational new drug met the appropriate standards of identity, strength, quality, and purity as needed for safety. The [ ] you administered to subjects was not confirmed to be sterile or free of pathogens. In addition, immunogenic potential and [ ] were not assessed.

   In your written response of January 5, 2005, you stated that due to your lack of manufacturing expertise, you relied on expert collaborators who informed you that [ ] and sterility testing were not usually required in studies such as this one. We note that [ ] and sterility were not the only concerns that should have been considered before administering this investigational new drug to human subjects. Our investigation found that the [ ] protein used to prepare the [ ] 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." By administering this drug without adequate prior evaluation of its infectious potential, you exposed subjects to unnecessary risks and failed to protect their rights, safety, and welfare.

3. You failed to obtain legally effective informed consent. [21 CFR 50.20].

As clinical investigator [21 CFR 312.60], you were responsible for obtaining the informed consent, in accord with 21 CFR Part 50, of each human subject to whom the investigational new drug [ ] was administered.

a. You failed to obtain informed consent that contained the required basic elements of informed consent. [21 CFR 50.25(a)]

i. The informed consent document (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 #2, 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.

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).

In your written response, dated January 5, 2005, you acknowledge that the ICD was inadequate.

b. In obtaining informed consent, you 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 specifically authorized use of [ ] in a 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 your written response, dated January 5, 2005, you acknowledge that this statement in the ICD was not correct.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational drugs.

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. In your written response, you have acknowledged the regulatory violations, however, you have failed to provide us with adequate assurances or corrective measures to prevent similar violations from recurring in the future. Failure to adequately and promptly respond 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