DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

David H. Vesole, M.D., Ph.D.
c/o Kathy L. Nusslock, Esq.
Davis & Kuelthan, s.c.
Suite 1400
Milwaukee, WI 53202

Ref: 07-HFD-45-0501

Dear Dr. Vesole:

Between March 10, 2006 and April 6, 2006, Mr. Scott Laufenberg representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of several clinical investigations you conducted while you were at the Medical College of Wisconsin, Milwaukee, WI, including:

**Protocol**[ ]Phase III Randomized, Double-Blind (Double Dummy) Study of the Safety, Tolerance and Efficacy of[ ]vs. Fluconazole in the Prophylaxis of Invasive Fungal Infections in High Risk Recipients of Allogenic Progenitor Cell Transplantation with Graft-Versus-Host Disease. The investigational new drug was[ ]and the sponsor was Schering-Plough Research Institute.

**Protocol**[ ]A Multicenter Randomized, Parallel-Group, Double-Blind, Placebo-Controlled Study of[ ]Plus Dexamethasone Alone in Previously Treated Subjects with Multiple Myeloma. The investigational new drug was[ ]and the sponsor was Celgene Corporation.

**Protocol Study**[ ]Phase I/II of Escalating-Dose[ ]with Autologous Pluripotent Hematopoietic Stem Cell Support and[ ]in Cancer Patients. The investigational new drugs were [ ]

This inspection is a part of the 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.

We are aware that the issued form FDA 483, Inspectional Observations has been reviewed by you. Your response dated May 18, 2006 submitted on your behalf by your attorney, Ms. Kathy Nusslock, has been reviewed.

From our review of the establishment inspection report, the documents submitted with that report, and the May 18, 2006 letter reply to the Form FDA 483, 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. Your May 18, 2006 letter fails to adequately address the violations. We are aware that at the conclusion of the inspection, Form FDA 483, Inspectional Observations was sent to you. We wish to emphasize the following:

1. **You failed to assure that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 was responsible for the continuing review and approval of the clinical investigation [21 CFR 312.66].**

   a. IRB approval of your research study,[ ]expired on March 17, 2004. Our investigation found that the IRB requested information from you on this study on February 18, 2004, before approving the study under continuing review. The requested changes were not submitted by you to the IRB until May 12, 2004, approximately two months after IRB approval had expired. IRB approval was not granted until May 19, 2004.

2. **You failed to adequately document informed consent [21 CFR 50.27].**

   Specifically,

   a. Our investigation failed to find documentation of informed consent for Subjects [ ]013 and[ ]/016 who participated in study[ ]

   b. Our investigation failed to find documentation of informed consent for Subject [ ]/007 who participated in study[ ]

3. **You failed to promptly report to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.66].**

   Our investigation found documentation of numerous serious adverse events in source documents that were not reported to the IRB in a timely manner. For example, in Protocol[ ]

| Subject | SAE | Date of SAE | Date SAE reported to the IRB |
|---|---|---|---|
| [ ]/008 | diarrhea | October 28, 2001 | July 22, 2002 |
| [ ]/663 | abdominal pain | August 9, 2002 | November 4, 2002 |
| [ ]664 | death | November 5, 2002 | December 12, 2002 |
| [ ]/003 | death | September 6, 2001 | October 10. 2001 |
| [ ]/015 | nausea, vomiting | July 25, 2001 | October 25, 2001 |

4. **You failed to promptly report to the study sponsor any adverse effect that may be reasonably regarded as caused by, or probably caused by, the drug [21 CFR 312.64(b)].**

   You failed to promptly report certain subject adverse effects to the sponsor. For example, in Protocol[ ]

| Subject | SAE | Date of SAE | Date SAE reported to the sponsor |
|---|---|---|---|
| [ ]/008 | diarrhea | October 28, 2001 | July 20, 2002 |
| [ ]/663 | abdominal pain | August 9, 2002 | November 4, 2002 |
| [ ]015 | nausea, vomiting | July 25, 2001 | August 28, 2001 |

5. **You failed to conduct the investigation in accordance with the investigational plan [21 CFR 312.60].** For example,

   a. Protocol[ ]

      i. Subjects[ ]/0010 and[ ]/006 were reported as not meeting the inclusion criteria, but were nevertheless enrolled in the study.

      ii. There were numerous protocol study procedures you failed to perform. Specific examples follow.

         1) Subject[ ]/00002 did not have fungal blood cultures at week 2, 6, and 16; at week 24 this subject did not have an oral swish and a neurological exam as required by the protocol.

         2) Subject[ ]0003 at weeks 4, 6, 8, and 10 did not have fungal blood cultures; at week 2 this subject did not have vital signs and laboratory assessments.

         3) Subject[ ]/0013 did not have pregnancy tests at week 8 and 16.

         4) Subject[ ]/0006 did not have hematology and chemistry profiles at week 6.

5) Subject[ ]/0008 did not have fungal blood cultures at weeks 4, and 24; at week 2 did not have an oral swish; at week 14 did not have vital signs; and at week 24 did not have a neurological exam.

6) Subject[ ]/0005 did not have fungal blood cultures at weeks 10, 12, 14, and 20; at week 4 did not have vital signs; at week 8 did not have a pregnancy test; and at week 16 did not have an oral swish.

7) Subject[ ]/664 did not have a pregnancy test at week 8.

8) Subject[ ]/0016 did not have a baseline CT Scan or MRI.

b. Protocol [ ]

i. You failed to perform numerous study procedures required by the protocol. For example,

1) Subject[ ]/4412 did not have not have temperature taken at the cycle 12 visit.

2) Subject[ ]/4005 did not have a weight determination at cycle 11.

3) Subject[ ]/4456 was not weighed on day 15, cycle 1.

4) Subject[ ]4028 did not have a height determination at the baseline visit and a pregnancy test, 24 hour urine, monoclonal paraprotein on Day 1, Cycle 1.

5) Subject[ ]/5269 did not have hematology and chemistry profiles on Day 8, Cycle 1.

6) Subject[ ]/4448 did not have a height determination at baseline and hematology and chemistry profiles on Day 8 Cycle 1.

7) Subject[ ]/4446 did not have a urinalysis, and 24 hour urine at baseline and on day 15, cycles 2 and 3.

8) Subject[ ]5473 did not have a height determination at baseline, a weight determination on day 1, cycle 2, and temperature determination at cycle 3.

9) Subject[ ]/4814 did not have height determination at baseline, a weight determination on day 15, cycle 2, and temperature determination at cycle 4.

10) Subject[ ]/5474 did not have vital signs and a height determination at baseline and hematology and chemistry profiles on day 8, cycle 1.

ii. You failed to discontinue dexamethasone as provided in the protocol, but reduced the dose by tapering for Subjects [ ]/4412,[ ]/4448,[ ]/4446, and[ ]/5473.

**6. You did not maintain adequate records of the disposition of the investigational new drug, including dates, quantities and use by subjects [21 CFR 312.62(a)].**

For protocol [ ]you failed to maintain study drug records sufficient to allow verification and reconciliation of study drug use by Subjects [ ]/0003, [ ]/0013,[ ]/0010,[ ]/0009,[ ]/0006,[ ]/0008,[ ]/0005,[ ]664, and [ ]/0011. Specifically, our investigation was unable to verify or reconcile study drug consumed by the subject with the data recorded in the CRFs.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of an investigational drug. It is your responsibility to ensure adherence to each requirement of the law and relevant FDA 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) working days of your 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 any questions, please contact Leslie Ball, M.D., at (240) 276-8840; FAX (240) 276-8844. 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}*

Gary Della'Zanna D.O., M.Sc.
Director
Division of Scientific Investigations, HFD-45
Office of Compliance
Center for Drug Evaluation and Research

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

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/s/
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Gary DellaZanna
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