



Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448
CBER - 03 - 009

By Mail
And by Facsimile Transmission

Warning Letter

APR 14 2003

Jacqueline M. Halton, M.D.
Children's Hospital of Eastern Ontario
402 Smyth Road
Ottawa, Ontario K1K 8L1

Dear Dr. Halton:

During the period from January 27 through 31, 2003, Patricia Murphy, an investigator with the Food and Drug Administration (FDA), reviewed your activities as a clinical investigator for the study "ANBL0032, Phase III Randomized Study of Chimeric Antibody 14.18 (Ch14.18) in High Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue." This is a Children's Oncology Group (COG) study that is sponsored by the Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health. The inspection was conducted as part of the FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of clinical research involving investigational drugs.

At the close of the inspection, a Form FDA 483, List of Inspectional Observations, was issued to and discussed with you. We have reviewed your response, dated February 25, 2003, to the Form FDA 483. Based upon the inspectional findings described in the Form FDA 483, and our subsequent review of documents collected during the inspection, we have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Part 312 (available at <http://www.access.gpo.gov/nara/cfr/index.html>). The applicable provisions of the CFR are cited for each violation listed below.

1. **You failed to protect the rights, safety, and welfare of subjects under your care and failed to ensure that the investigation was conducted according to the investigational plan. [21 CFR § 312.60].**

You failed to protect the rights, safety, and welfare of subjects when you administered overdoses of the study drug Interleukin-2 (IL-2) that were 22 to 25 times higher than the dose specified in the protocol. Overdoses were given to both subjects enrolled in this arm of the study [] and []. As a result of the overdoses, both subjects suffered adverse events, and one [] died.

- A. The inspection revealed that you administered [] micrograms of IL-2 per day for four days to subject [] beginning on July 23, 2002. This was 22 times higher than the correct protocol dose of [] micrograms per day.

This subject developed numerous adverse events presumed to be secondary to the study drug, including fever, lethargy, and a skin rash. The COG Study Chair for the protocol was notified. She characterized the reaction as idiosyncratic, and decided to discontinue administration of IL-2 to the subject.

- B. The inspection revealed that you administered [] micrograms of IL-2 per day for four days to subject [] beginning on September 16, 2002. This was 25 times higher than the correct protocol dose of [] micrograms per day. The subject developed hypotension, fever, and a rash. However, those adverse events resolved before the subject returned for the next administration of IL-2. Beginning on September 23, 2002, you administered a second course of IL-2, [] micrograms per day, for over two days. This was 25 times higher than the second dose described in the protocol, [] micrograms per day.

The subject developed adverse events which included: anemia, thrombocytopenia, abdominal pain, adult respiratory distress syndrome, pulmonary edema, disseminated intravascular coagulation, myocardial dysfunction, hepatic dysfunction, ascites, CNS irritability, and hallucinations. Systemic inflammatory response syndrome, with a massive capillary leak, was diagnosed. The subject's condition deteriorated, and he died on []

We note that the CHEO pre-printed patient order form states that the first dose of IL-2 is [] micrograms/kilograms/day. However, as described in the protocol, the dosage should have been [] micrograms/meters²/day instead of [] micrograms/kilograms/day (emphasis added). This is a serious deviation. While the CHEO COG subcommittee, of which you are a member, approved the use of this incorrect form, it remains your responsibility as the clinical investigator to assure adherence to the protocol-specified dosing regimen.

During the inspection, you provided a copy of a revised CHEO pre-printed patient order form for this study. In your letter, dated February 25, 2003, you said that the CHEO pre-printed order template has been changed to correct the noted error. Furthermore, the drug dose entered into the pre-printed template will be in the units specified in the protocol, and not in micrograms. Two physicians, as well as the CHEO COG Subcommittee, will review the template. Two clinicians will independently calculate future doses.

Your corrective action appears to be adequate to prevent future IL-2 dosing errors.

2. You failed to ensure that the investigation was conducted according to the investigational plan. [21 CFR § 312.60].

A. The inspection revealed that you failed to document a hospitalization for subject [] as required by the COG Remote Data Entry System Case Report Form (CRF) entitled *Study ANBL0032: Reporting Period Receipt*. The subject was admitted to the hospital with fever on May 2, 2002. She was treated with Cefazidime, pending culture results, and then discharged on May 4, 2002. However, for the entry "Number of days hospitalized," the CRF said zero. During the inspection, the CRF was corrected to reflect three days of hospitalization.

B. You failed to submit the subject data CRFs called "Roadmaps" to the COG Operations Center within one week of completion of each course of therapy, as required by the protocol. Instead, they were submitted up to 4 months after the required dates.

In your letter, dated February 23, 2002, you said that your institute will hire additional personnel to assure that study staff will submit the required reports on time.

Your proposed corrective action appears to be adequate if the additional personnel and study staff receive appropriate training and adhere to established procedures.

C. You failed to ensure that three study drugs (Chimeric monoclonal antibody 14.18, GM-CSF, and IL-2) were stored at the required temperature to ensure the drugs maintained their specified characteristics. There is no documentation to show that the study drugs were in a refrigerator maintained at 2 to 8 degrees Centigrade. At the conclusion of the inspection, you provided a copy of the Refrigerator Temperature Log from January 29 to 31, 2003.

In your letter, dated February 23, 2002, you said that a thermometer is now in the refrigerator in the satellite pharmacy and a record log is now recorded on a daily basis.

Your proposed corrective action appears to be adequate provided the thermometer is properly maintained and the log properly completed.

Please address the following items in your written response to this letter:

1. Please provide a copy of the final report from the CHEO Special Protocol Review Committee that was formed to review the overdoses of IL-2.
2. An autopsy report for subject [] was not available at the time of the inspection. Please provide a copy of the autopsy report for this subject when it becomes available.

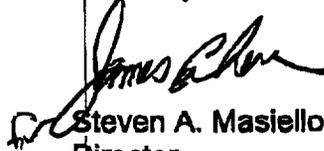
This letter is not intended to be an all-inclusive list of deficiencies.

This Warning Letter is issued to you because of the serious nature of the observations noted at the time of the FDA inspection. Please be advised that the failure to effectively put into practice the corrective actions you have described in your response letter, and/or the commission of other violations may warrant the initiation of enforcement actions without further notice. These actions could include initiation of clinical investigator disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs, and/or injunction.

Please submit your response to the address below. If you have any questions about the contents of this letter, you may contact:

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Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research