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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
9200 Corporate Boulevard  
Rockville, Maryland 20850

**WARNING LETTER**

VIA FEDERAL EXPRESS

**JAN 28 2008**

Marin H. Kollef, M.D.  
Pulmonary and Critical Care  
Washington University School of Medicine  
660 South Euclid Avenue, Box 8052  
St. Louis, Missouri 63110-1010

Dear Dr. Kollef:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from August 7 to August 15, 2007, by an investigator from the FDA Kansas City District Office. The purpose of this inspection was to determine whether activities and procedures related to your participation in the clinical study [redacted] and the [redacted], complied with applicable federal regulations. [redacted] is a device, as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your written response, dated September 26, 2007, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for IDE, Premarket Approval (PMA) applications, and Premarket Notification submissions (510(k)) are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 C.F.R.), Part 812 -- Investigational Device Exemptions, Part 50 -- Protection of Human Subjects, and Section 520(g) (21 U.S.C. 360j(g)) of the Act. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 to Mr. James Moran in

your absence, and discussed the observations listed on the form with Mr. Moran and Ms. Ann Doyle. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

**Failure to obtain informed consent in accordance with the regulations regarding the protection of human subjects [21 CFR 50.20, 50.23, 50.27, 812.100, 812.110(b), and 812.140(a)(3)(i)].**

Pursuant to the above stated regulations, an investigator must ensure that informed consent is obtained in accordance with 21 CFR 50.20, and maintain accurate, complete, and current records, including documentation of informed consent. Examples of your failure to adhere to the above stated regulations include, but are not limited to, the following:

1. The Institutional Review Board (IRB) approved informed consent documents for six subjects lack dates and signatures of study participants. There is no evidence that subjects were legally consented prior to enrollment in the study and no written concurrence of a licensed physician and brief description of the circumstances justifying the failure to obtain informed consent. Examples of subjects who  without informed consent include the following:

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- and

The study sponsor notified you of the above stated deficiencies on May 12, 2003; however, you continued to fail to obtain informed consent from later subjects or the subjects' legally authorized representatives. Examples of this continued failure include the following subjects:

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- and

2. The IRB-approved informed consent document included a study flow sheet. You included this flow sheet for subjects who were given the March 28, 2003 IRB-approved revision of the informed consent document. However, the informed consent forms you used with subjects prior to March 28, 2003 lacked the flow

sheet that is referred to in both the original, July 24, 2002 and revised, February 18, 2003, IRB-approved consent documents. Nineteen subjects were enrolled prior to March 28, 2003 and were consented using consent forms that lacked the flow sheet. Some examples include, subjects [redacted], and [redacted].

In some cases, you attribute the lack of legally effective informed consent to oversights by study personnel. In the summary section of your response you stated, "To address this concern going forward we will require the entire study team to go through an additional training program specific to the process of obtaining and documenting informed consent. This program will also focus on obtaining consent in a [redacted] setting. . ." Your response is inadequate in that it does not state a timeline for this training.

**Failure to ensure that an investigation is conducted according to the signed agreement, investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA [21 CFR 812.100 and 812.110(b)].**

Pursuant to 21 CFR 812.100 and 812.110(b), an investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, investigational plan, applicable FDA regulations, and any conditions of approval imposed by an IRB or FDA. You failed to adhere to the above-stated regulations. In the section, [redacted]

[redacted]" the protocol states, "[redacted]  
[redacted]" Later, in the [redacted] section, the protocol states, "Prior to the procedure, the Investigator must explain to each subject (or the subject's legally authorized representative . . ."

You allowed personnel to perform study-related functions they were not authorized to perform under the investigational plan. The study personnel identification list specifies all individuals involved in the study and their authorized functions. It clearly identifies who is authorized to consent individuals for participation in the study and includes their title, signature, and date of authorization. Ten subjects were consented by individuals not listed on the study personnel identification list. Examples of subjects who were consented by unauthorized individuals include the following: [redacted].

In your response, you indicate that you supervised training of all study personnel who obtained informed consent for the study, and you attribute the missing signatures on the delegation of authority logs to an oversight. You indicated that you will ensure that all individuals trained under the protocol also will have documentation, through proper completion and signing of the delegation of authority log. Your response is inadequate in that you have not indicated when this training will be completed. Your response describes cases in which you obtained "verbal consent." However, under 21 CFR 50.27, informed consent must be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized

representative, unless the IRB waives the requirement or finds that the requirements in 21 CFR 50.24 for an exception from informed consent are met.

No "verbal consent" was approved by the IRB. Please work with your IRB to develop a plan for notifying subjects for whom informed consent was not obtained and documenting notification that they [redacted], as well as a plan for obtaining informed consent to prevent future recurrences of this problem. Please provide us with documentation of a corrective action plan that addresses each of the violations noted above. Your plan should include:

- written procedures for ensuring study protocol compliance
- written verification of staff training on study procedures and requirements, and/or
- internal study reviews or audits.

Your corrective action plan should include sufficient information to confirm that such protocol violations have not occurred with other subjects and/or studies, and how corrective actions have been implemented to prevent recurrence of the problems in future studies. Please include with your response any new or amended procedures, implementation dates, and/or training of study personnel.

The violations described above are not intended to be an all-inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the additional actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are a clinical investigator. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21 C.F.R. 812.119.

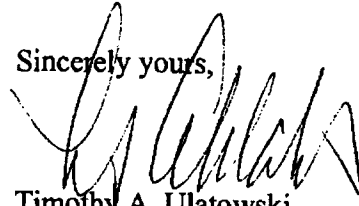
You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Attention: Ms. Linda Godfrey, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 9200 Corporate Boulevard, HFZ-310, Rockville, Maryland 20850.

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A copy of this letter has been sent to the FDA Kansas City District Office. Please send a copy of your response to that office, at 11630 W. 80<sup>th</sup> Street, Lenexa, Kansas, 66214.

If you have any questions, please contact Ms. Linda Godfrey at (240) 276-0125 or [Linda.Godfrey@fda.hhs.gov](mailto:Linda.Godfrey@fda.hhs.gov).

Sincerely yours,

A handwritten signature in black ink, appearing to read "Timothy A. Ulatowski". The signature is fluid and cursive, with a large initial "T" and "U".

Timothy A. Ulatowski  
Director  
Office of Compliance  
Center for Devices and  
Radiological Health