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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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WARNING LETTER
Via Federal Express

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Mitchel A. Kling, M.D.
National Institutes of Health
10 Center Drive
Building 10, Room 2D46
MSC 1284
Bethesda, Maryland 20892

Dear Dr. Kling:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of the clinical trials which were conducted at the Veterans Administration (VA) Medical Health Care System in Baltimore, MD for which you were the clinical investigator until April 16, 2004. This letter also discusses a response from Anthony F. Lehman, M.D., Department of Psychiatry, University of Maryland Health Care System, who is presently the clinical investigator for those studies requiring continued subject follow-up, and requests a prompt response from you. Ms. Lynette Salisbury, an investigator from FDA's Baltimore District Office, conducted the inspection from July 19 through August 17, 2004. The purpose of the inspection was to determine if your activities as the clinical investigator for several studies sponsored by [REDACTED] complied with applicable FDA regulations. These studies include use of the [REDACTED] (stands for [REDACTED]) for the treatment of [REDACTED]; an amendment to that study to permit [REDACTED] assessment interviews for [REDACTED] subjects; a further amendment to study the [REDACTED] subjects undergoing treatment with the [REDACTED] and a long-term study of standard-of-care treatment of subjects with [REDACTED] which you intended to compare to outcomes of the [REDACTED] study ([REDACTED]); The [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)].

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification [510(k)] submissions 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 CFR) Part 812, Investigational Device Exemptions; Part 50, Protection of Human Subjects; and the Act. At the close of the inspection, Ms. Salisbury presented a Form FDA 483, "Inspectional Observations," to Dr. Lehman for review and discussed the listed deviations. Dr. Lehman addressed each of the observations in his letter of September 10, 2004, which was addressed to Mr. Lee Bowers, Baltimore District Director. His response notes that all of the observations recorded by Ms. Salisbury were correct and that corrective actions have been implemented to prevent reoccurrence during the remaining follow-up of study subjects. The deviations noted on the Form FDA 483, Dr. Lehman's response, and our subsequent inspection report review are discussed below.

Failure to submit progress reports to the institutional review board (IRB) at regular intervals or at least yearly (21 CFR 812.150(a)(3)); Failure to ensure that the investigation is conducted in accordance with applicable FDA regulations (21 CFR 812.100, 812.110(b) and with conditions of IRB approval (21 CFR 812.110(b))

Pursuant to 21 CFR 812.150(a)(3), an investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB in regular intervals but no less often than yearly. Your reviewing IRB required such reports to be submitted no less than 30 days prior to the one year anniversary of its most recent approval of the study, so that it could review this report and determine whether to permit continuation of the study. You failed to adhere to 812.150(a)(3) and to the IRB's timelines, and as a result of your failure to submit timely progress reports, the [REDACTED] study of the [REDACTED] [REDACTED] suffered lapses in IRB approval. Pursuant to 21 CFR 56.109(f), an IRB is required to perform continuing review of all studies at regular intervals, depending upon the degree of risk involved to subjects, but no less than yearly. The required study progress reports from the clinical investigator provide the basis for this continuing review. (The regulation relating to IRBs is found at 21 CFR Part 56 and is entitled "Institutional Review Boards.") As a result of your failures to submit timely progress reports, you also failed to ensure that the study was conducted in accordance with the applicable FDA regulations regarding continuing IRB review and the IRB's own conditions of approval.

Failure to conduct the study according to the investigational plan (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, the investigational plan, and applicable FDA regulations. Several instances of deviations from the investigational plan were noted, including but not limited to the following:

- use of a commercial lead for a subject implant in lieu of the investigational lead;
- programming of the device on Visit 1 after implantation for two (2) subjects in the acute stage of the study, while the protocol called for programming on the

- second post-implantation visit;
- other failures to program the device according to the investigational plan. For example, one subject received adjustments on Visits 5 & 6, although the protocol called for all adjustments to be made on Visits 2-4, and another subject's device was programmed to increase amplitude by substantially larger increments than called for by the protocol.

Failure to document informed consent by use of a written consent form approved by the IRB (21 CFR 50.27(a))

Pursuant to 21 CFR 50.27(a), informed consent must be documented through the use of current, IRB-approved consent forms. You failed to adhere to this requirement in that thirteen (13) subjects in the [REDACTED] signed a form that had not been approved by the IRB to allow videotaping of the [REDACTED] assessment interviews. All thirteen subjects signed this form prior to the March 21, 2001, IRB approval of the informed consent form for this [REDACTED]. Dr. Lehman's response notes that all thirteen later signed an approved consent form. We note as well that you videotaped these subjects prior to IRB approval of the protocol amendment that permitted videotaping this assessment, and thus the taping itself constituted a deviation from the approved investigational plan.

The deviations described above are not intended to be an all-inclusive list of deficiencies that may have occurred in your study. It is your responsibility as a clinical investigator to comply with applicable regulations.

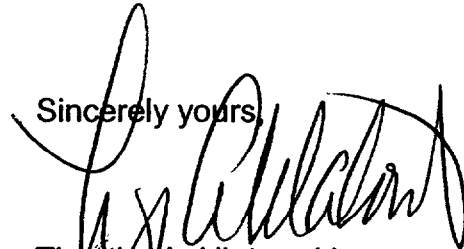
Within fifteen (15) working days after receiving this letter please provide written documentation of the specific steps you have taken or will take to assure that the violations noted during this study will not be repeated in any future studies for which you are the clinical investigator. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. FDA may also initiate proceedings to disqualify you from further activity as a clinical investigator, in accordance with 21 CFR 812.119. Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Viola Sellman, Chief, Program Enforcement Branch.

We are also sending a copy of this letter to FDA's Baltimore District Office, 600 Metro Drive, Suite 101, Baltimore, Maryland 21215, and request that you also send a copy of your response to that office. If you have any questions please contact Ms. Sellman at the address listed above or by telephone at (240) 276 - 0125.

In addition to the violations noted above, we write to express concern about the fact that your subject files for the [REDACTED] study contained information about a number of

adverse events that were not recorded on the case report forms. As sponsors receive and rely primarily on the case report forms for their information about the study, the failure to include information in those CRFs, even where it is present in the underlying source documentation required as a part of the broader case history record (see 21 CFR 812.140(a)(3)), can result in sponsors and ultimately FDA receiving a distorted picture of the performance of the device.

Sincerely yours,



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

cc:

Anthony F. Lehman, M.D.
University of Maryland Health Care System
Department of Psychiatry
701 W. Pratt Street
Room 388
Baltimore, Maryland 21201

Kristina C. Borrer, Ph.D.
Director
Division of Compliance Oversight
Office of Human Research Protections
Department of Health and Human Services
The Tower Building
1101 Wootton Parkway, Suite 200
Rockville, Maryland 20850

Donald Rosenstein, M.D.
Chair
Institutional Review Board
National Institute of Mental Health
National Institutes of Health
9000 Rockville Pike
Bethesda, Maryland 20892