DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NOTICE OF OPPORTUNITY FOR HEARING (NOOH)

HAND DELIVERY

Emanuel Calenoff, M.D.
(b) (6) (Home Address)

04/10/2015

Dear Dr. Calenoff:

The Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA) has information indicating that you repeatedly or deliberately violated federal regulations in your capacity as a sponsor-investigator in a clinical trial with an investigational drug. These violations provide the basis for withdrawal of your eligibility as a clinical investigator to receive investigational new drugs.

CDER's findings are based on information obtained during an FDA inspection, discussed below, of the following clinical study for which you were the sponsor-investigator of record:

> Clinical investigation of the investigational drug mimotopic peptide immunotherapy, described in the article "Mimotopic peptide immunotherapy for the treatment of multiple sclerosis, an inflammatory autoimmune disease," which was published in the October 30, 2013 issue of the *American Journal of Clinical and Experimental Immunology*.

FDA conducted an inspection between May 19 and May 22, 2014. After the inspection, and pursuant to section 312.70(a) of Title 21 of the Code of Federal Regulations [21 CFR 312.70(a)], the CDER informed you by letter entitled, "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" (NIDPOE) dated September 25, 2014, of the specific matters complained of, and offered you an opportunity to respond in writing or at an informal conference. The NIDPOE also offered you the option of entering into a consent agreement with FDA, thereby terminating any administrative proceeding against you. In response to the NIDPOE, you submitted additional documentation dated November 14, 2014.

After a review of all available information, the CDER has concluded that your written explanations are unsatisfactory because they fail to adequately address the violations set forth below. Accordingly, you are being offered an opportunity for a regulatory hearing pursuant to 21 CFR parts 16 and 312, to determine whether you are entitled to receive test articles as set forth under 21 CFR 312.70. You have the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in 21 CFR part 16 and by FDA's guidelines on electronic media coverage of administrative proceedings, 21 CFR part 10, subpart C. Enclosed you will find copies of these regulations.

A listing of the specific violations follows. These are matters that would be considered at the regulatory

hearing, if granted. Applicable provisions of the CFR are cited for each violation.

1. **You failed to submit an IND for the conduct of a clinical investigation with an investigational new drug that is subject to 21 CFR 312.2(a) [21 CFR 312.20(a) and 312.40(a)].**

   In relevant part, the Federal Food, Drug, and Cosmetic Act (FD&C Act) defines the term *drug* as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or function of the body of man or other animals" [21 U.S.C. 321(g)].

   The abstract section of your study "Mimotopic peptide immunotherapy for the treatment of multiple sclerosis, an inflammatory autoimmune disease" states, "The study encompassed serological testing to confirm the IgE-positive status of the MS [multiple sclerosis] patient and negative status of the controls, an eight month course of peptide-based immunotherapy, and assessment of therapeutic efficacy and potentially adverse effects." Because you were studying whether mimotopic peptide immunotherapy treats multiple sclerosis, mimotopic peptide immunotherapy meets the definition of a drug under the FD&C Act.

   To market a new drug lawfully, a sponsor must obtain approval of a new drug application or abbreviated new drug application under Section 505 of the FD&C Act [21 U.S.C. 355]. An Investigational New Drug application (IND) is the means by which a sponsor obtains an exemption from this requirement to distribute an investigational drug [21 U.S.C. 355(i)]. FDA regulations require a sponsor to submit an IND application before conducting a clinical investigation of a drug in human subjects, unless the clinical investigation qualifies for an IND exemption.

   A marketed drug product is exempt from the IND requirements if all of the following exemption criteria are met:

   - The drug product is lawfully marketed in the United States;
   - The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use and there is no intent to use the investigation to support any other significant change in the labeling of the drug;
   - In case of a lawfully marketed prescription drug, the investigation is not intended to support a significant change in the advertising for the drug;
   - The investigation does not involve a route of administration, dosage level, use in a patient population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
   - The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR Part 56 and with the requirements for informed consent set forth in 21 CFR Part 50; and
   - The investigation is conducted in compliance with the requirements of 21 CFR 312.7 regarding promotion of investigational drugs.

A person planning to conduct a bioavailability or bioequivalence study of an unapproved version of an approved drug product is not required to submit an IND when certain criteria under 21 CFR 320.31 are met.

Your investigational drug, mimotopic peptide immunotherapy, is not a lawfully marketed drug product in the United States, nor is it an unapproved version of an approved drug product undergoing a bioavailability or bioequivalence study. As a result, before using mimotopic peptide immunotherapy in a clinical investigation, you were required to submit an IND for the drug to FDA, and the IND was required to go into effect under 21 CFR 312.40.

You failed to submit an IND before conducting the study "Mimotopic peptide immunotherapy for the treatment of multiple sclerosis, an inflammatory autoimmune disease."

During the inspection, you acknowledged that you did not submit an IND application to the FDA before initiating the study noted above.

In your response to the NIDPOE letter, you did not address your failure to submit an IND for the conduct of a clinical investigation with an investigational new drug that is subject to 21 CFR 312.2(a).

2. You failed to retain adequate records of the disposition of the drug [21 CFR 312.57(c) and 312.62(c)].

As the sponsor of the study noted above, you were required to retain records showing the receipt, shipment, or other disposition of the investigational drug, mimotopic peptide immunotherapy. In addition, as the clinical investigator for the study noted above, you were required to retain records of the disposition of the drug, including dates, quantity, and use by subjects.

You failed to adhere to these requirements. Specifically, you failed to retain records of drug disposition for the six subjects into whom you injected mimotopic peptide immunotherapy subcutaneously over an eight-month period.

During the inspection, you indicated that you synthesized the investigational drug at your residence, using components that you purchased from [redacted] (b) (4). However, you did not have records showing the receipt, shipment, or other disposition of the investigational drug, as required by 21 CFR 312.57(c). You also indicated that you administered all injections of the investigational drug to the six subjects at your residence. However, you did not have records showing the disposition of the investigational drug, including dates, quantity, and use by subjects, as required by 21 CFR 312.62(c).

During the inspection, you stated that you had no drug accountability records for the FDA investigator to review. You also stated that study records were scanned into your computer and stored on its hard drive; however, you indicated that one week before the inspection, your computer crashed during a thunderstorm, all study records on the computer's hard drive were lost, and no hard copies were available. Because no hard copies or electronic back-up copies of the study records were available, you have violated the requirements to retain drug disposition records.

In your response to the NIDPOE letter, you stated, "I believe that my singular fault was in inadequate record keeping which relied solely on computer storage." You stated that your computer was

frequently subject to computer viruses and crashes which may have caused the ablation of files. You indicated that since the time of the inspection, you amended your daily computer checks for viruses.

Your response is unsatisfactory because it does not adequately address your failure to retain adequate records of the disposition of the drug, specifically the retention of hard copies or electronic back-up copies of study records.

Your failure to retain adequate records of the disposition of the drug compromises the validity and integrity of the data that you generated.

3. **You failed to retain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(c)].**

As a clinical investigator for the study noted above, you were required to retain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. In addition, the case history for each individual shall document that informed consent was obtained before participation in the study.

You failed to adhere to these requirements. Specifically, you failed to retain case histories, including documentation of informed consent, for the six subjects into whom you injected mimotopic peptide immunotherapy subcutaneously over an eight-month period. Signed informed consent documents (ICDs) were not available to assess whether these subjects were properly consented before their enrollment in the study.

During the inspection, you indicated that you "did not keep any source records" for this study. You also stated that signed ICDs were obtained from subjects enrolled in this study, but you did not have signed ICDs available for review. You indicated that signed ICDs were scanned into your computer but were lost when the computer crashed one week before the inspection, and no hard copies were available. Because no hard copies or electronic back-up copies of the study records were available, you have violated the requirement to retain signed ICDs.

In your response to the NIDPOE letter, you stated, "I believe that my singular fault was in inadequate record keeping which relied solely on computer storage." You stated that your computer was frequently subject to computer viruses and crashes which may have caused the ablation of files. You indicated that since the time of the inspection, you amended your daily computer checks for viruses.

Your response is unsatisfactory because it does not adequately address your failure to retain adequate and accurate case histories, specifically the retention of hard copies or electronic back-up copies of study records.

Your failure to retain adequate and accurate case histories, including documentation of informed consent, compromises the validity and integrity of the data captured at your site, and raises concerns about whether subjects had adequate opportunity to assess the risks and benefits of their participation in the study.

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

   As a clinical investigator, you are required to assure that an IRB that complies with 21 CFR Part 56 reviews and approves a proposed clinical investigation. Among other requirements, Part 56 requires that each IRB in the United States that reviews clinical investigations regulated by FDA and intended to support applications for research or marketing permits for FDA-regulated products must register at a site maintained by the Department of Health and Human Services [21 CFR 56.106(a)]. Additionally, each IRB shall have at least five members, sufficiently qualified through experience and expertise, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution [21CFR 56.107(a)]. You failed to ensure that an IRB that complies with 21 CFR Part 56 reviewed and approved your proposed clinical study.

   Specifically, you failed to ensure that an IRB approved your study, "Mimotopic peptide immunotherapy for the treatment of multiple sclerosis, an inflammatory autoimmune disease," before the enrollment of six subjects. IRB documents, including records of IRB approval and IRB-approved consent documents, were not available to confirm that an IRB reviewed and approved this study before the subjects' enrollment.

   During the inspection, you stated that you assembled "regular folks" to act as the IRB for this study. You also stated that this IRB was located in Texas, but you could not recall the name of the IRB or the names and backgrounds of the individuals serving on the IRB. You indicated that you did not have any records of IRB review and approval of the study, including IRB approval of consent documents and progress reports to the IRB, because you stored the records on your computer and it crashed during a thunderstorm one week before the inspection.

   Your response to the NIDPOE letter did not address your failure to assure that an IRB was responsible for the initial and continuing review and approval of the proposed clinical study. Specifically, you have not provided any documentation that an IRB reviewed and approved this study before the subjects' enrollment.

Your request for a hearing must be made in writing within ten (10) business days after receipt of this letter, and should be directed to Scott J. MacIntire, Director, Division of Enforcement, Office of Enforcement and Import Operations, ORA, FDA, 10903 New Hampshire Avenue, WO32-4360, Silver Spring, MD 20993, Telephone (301) 796-8203, FAX (301) 847-8635. If no response to this letter is received by that time, you will be deemed to have waived any right to a regulatory hearing, and a decision in these matters will be made based on the facts available to FDA. No hearing will be held.

A request for a hearing may not rest upon mere allegations or denials, but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that no genuine and substantial issue of fact has been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

If you wish to respond but do not desire a hearing, you should contact Scott J. MacIntire within the specified time period and send a written reply containing your reply. The letter should state that you waive your right to a hearing, and that you want a decision on the matter to be based on your written response and other information available to FDA.

FDA's offer for you to enter into a consent agreement, attached to the NIDPOE dated September 25, 2014, remains available. Entering into a consent agreement would terminate the administrative procedures but would not preclude the possibility of a corollary judicial proceeding.

No final decision by FDA has been made at this time on your eligibility to continue to receive test articles as set forth under 21 CFR 312.70. Moreover, there will be no prejudgment of this matter if you decline to enter into a consent agreement and decide instead either to request a regulatory hearing or to request that the decision be based on information currently available to FDA.

Please inform Scott J. MacIntire within ten (10) business days whether you wish to request a hearing or to have this matter resolved by consent agreement or information available to FDA.

Sincerely,

/s/
Melinda K. Plaisier
Associate Commissioner for Regulatory Affairs

Enclosures:
21 CFR Part 10, subpart C
21 CFR Part 16
21 CFR 312.70
Consent Agreement