NOTICE OF INITIATION OF DISQUALIFICATION PROCEEDINGS AND OPPORTUNITY TO EXPLAIN (NIDPOE)

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

September 25, 2014

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

Dear Dr. Calenoff:

Between May 19 and May 22, 2014, Mr. Joel Martinez, representing the U.S. Food and Drug Administration (FDA), conducted an inspection to review your conduct of a 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*.

This inspection is a part of the FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Mr. Martinez presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We note that you have not provided a written response to the Form FDA 483.

We have reviewed the inspection report, the documents submitted with that report, and your affidavit dated May 22, 2014. Based on our evaluation of this information, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products, as published under Title 21, Code of Federal Regulations (CFR), part 312.70 (copy enclosed).

This letter provides you with written notice of the matters complained of and initiates an administrative proceeding, described below, to determine whether you should be disqualified from eligibility to receive test articles as set forth under 21 CFR 312.70 and disqualified from eligibility

to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.

A listing of the violations follows. The 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.

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 (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.

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.

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 a 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.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational products. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above-listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations, which placed unnecessary risks to human subjects and jeopardized the integrity of data, and FDA proposes that you be disqualified as a clinical investigator. You may reply to the above-stated findings, including an explanation of why you should not be disqualified as a clinical investigator, either in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.

Within fifteen (15) days of your receipt of this letter, write to me at the address below or call me at 301-796-3865 to arrange a conference time or to indicate your intent to respond in writing.

Should you choose to respond in writing, your written response should be forwarded within thirty (30) days of your receipt of this letter.

Your reply should be sent to:

Sean Y. Kassim, Ph.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5346
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above-listed violations. You should bring with you all pertinent documents, and a representative of your choice may accompany you. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The FDA's Center for Drug Evaluation and Research (the Center) will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered a regulatory hearing before FDA, pursuant to 21 CFR 16 (copy enclosed) and 21 CFR 312.70. Before such a hearing, FDA will provide you with notice of the matters to be considered, including a comprehensive statement of the basis for the decision or action taken or proposed, and a general summary of the information that will be presented by FDA in support of the decision or action. A presiding officer who has not participated in this matter will conduct the hearing. After such hearing, the Commissioner will determine whether you will remain entitled to receive test articles and to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by the FDA.

You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

To enter into the enclosed consent agreement with FDA, thereby terminating this disqualification process, you must:

(1) Initial and date each page of this Agreement;
(2) Sign and date the last page of this Agreement; and
(3) Return this Agreement initialed, signed, and dated to the signer below.

A copy of the fully executed Agreement will be mailed to you.

Sincerely yours,

/Sean Y. Kassim, Ph.D./
Sean Y. Kassim, Ph.D.
Acting Director
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosures:
#1 - Consent Agreement
#2 - 21 CFR 16
#3 - 21 CFR 312.70