DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NOTICE OF OPPORTUNITY FOR HEARING (NOOH)

Hand delivered by Andrea Branch on March 4, 2009

Arthur Ericsson, M.D.
6655 Travis St., Suite 820
Houston, TX 77030

Dear Dr. Ericsson:

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

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

> Protocol (b) (4) entitled "Evaluation of (b) (4) for the therapy of autoimmune/inflammatory conditions involving the nervous system," of the investigational drug (b) (4), performed for (b) (4).

FDA conducted an inspection between March 22 and April 18, 2007. 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 Center informed you, by letter titled "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" (NIDPOE) dated March 31, 2008, 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 June 25, 2008.

After a review of all available information, the Center has concluded that your written explanations are unacceptable 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 investigational new drugs. 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 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 will be considered at the regulatory hearing. Applicable provisions of the CFR are cited for each violation.

1) **You failed to comply with the requirements for use of an investigational new drug in a clinical investigation by administering the investigational new drug (b) (4) to subjects without an investigational new drug application (IND) in effect. [21 CFR 312.40]**

FDA regulations (21 CFR part 312) contain procedures and requirements governing the use of investigational new drugs. 21 CFR 312.3(b) defines a clinical investigation as "any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice." (b) (4) is not approved for marketing in the U.S.A; therefore, any clinical investigation involving the use of (b) (4) must meet the general requirements for use of an investigational new drug in a clinical investigation. An investigational new drug may be used in a clinical investigation if the following conditions are met: the sponsor submits an IND for the drug to FDA, the IND is in effect under FDA regulations, and the sponsor complies with all applicable requirements of 21 CFR parts 50, 56, and 312; and each participating investigator conducts his investigation in compliance with the requirements of 21 CFR parts 50, 56, and 312. [21 CFR 312.40(a)]

According to 21 CFR 312.40(b), an IND goes into effect thirty days after FDA receives the IND, unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold, or on earlier notification by FDA that the clinical investigations in the IND may begin. On December 19, 2006, (b) (4). submitted an IND for this product. Within thirty days of the IND submission and without receiving any notification from FDA that the clinical investigation might begin, you administered the investigational new drug to at least six subjects (b) (4) 1909 (January 3, 2007); (b) (4) 1906 (January 4, 2007); (b) (4) 1907 and (b) (4) 1912 (January 8, 2007); (b) (4) 1908 (January 10, 2007); and (b) (4) 1916 (January 15, 2007)]. Therefore, you violated 21 CFR 312.40(a) by administering the investigational new drug (b) (4) to subjects without an IND in effect.

Your written response and attachments did not address this violation. You attached an August 16, 2006, letter from (b) (4) approving the compassionate use of (b) (4). This letter does not address your failure to comply with the regulations described above. There are certain FDA regulations that allow for the administration of an investigational drug without meeting the above referenced requirements,

for example by obtaining a treatment IND or authorization for emergency use of an IND. See 21 CFR 312.34 and 21 CFR 312.36. However, you did not provide any evidence indicating that you submitted or received approval for a treatment IND under 21 CFR 312.34. Nor does it appear that (b) (4) could have met the requirements for a treatment IND, as the drug was not under investigation in a controlled clinical trial under an IND in effect for the trial. See 21 CFR 314.34(b)(iii). In addition, you did not provide any evidence indicating that you received authorization to administer (b) (4) through the emergency use of an IND under 21 CFR 314.36.

2) **You violated a clinical hold by giving subjects (b) (4) after FDA issued an order to delay the proposed clinical investigation. [21 CFR 312.42].**

A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. The clinical hold order may apply to one or more of the investigations covered by an IND. When a proposed study is placed on clinical hold, subjects may not be given the investigational drug. When an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; patients already in the study should be taken off therapy involving the investigational drug unless specifically permitted by FDA in the interest of patient safety. [21 CFR 312.42(a)]

The IND submission for the (b) (4) clinical investigation was placed on full clinical hold because insufficient information was submitted to allow FDA to assess risks to human subjects in the proposed study [see 21 CFR 312.42(b)(2)(i), specifically 312.42(b)(1)(iv)]. (b) (4) was notified of the clinical hold via telephone on January 25, 2007, and was sent a clinical hold letter on March 15, 2007. You were aware of the full clinical hold status for this investigation and the reason for the hold, as you provided the FDA investigator with a copy of the full clinical hold letter and you told the FDA investigator that (b) (4). notified you of the clinical hold in late January, 2007.

You violated the clinical hold order by administering (b) (4) to at least five subjects on multiple occasions [1907 (February 5 and 23, 2007), 1912 (January 29, 2007 and February 12, 2007), 1921 (February 27 and 28, 2007), 1924 (March 13 and 14, 2007), and 1928 (January 30, 2007, February 6, 13, and 20, 2007, and March 1 and 14, 2007)] after you were informed that the IND submission for this product was placed on clinical hold.

Your written response and attachments did not address this violation.

3) **You failed to obtain informed consent in accordance with the provisions of 21 CFR parts 50 and 56, as required by 21 CFR 312.60 and 312.66.**

Informed consent must be documented by the use of a written consent form approved by an Institutional Review Board (IRB) and signed and dated by the subject or the subject's legally

authorized representative at the time of consent [21 CFR 50.27, see 21 CFR 312.60]. As an investigator, it is your responsibility to use an informed consent form approved by an IRB in compliance with the requirements of 21 CFR part 56 [see 21 CFR 312.66]. Except as provided in 21 CFR 50.23 and 50.24, no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative [21 CFR 50.20]. In seeking informed consent, FDA regulations require that the following information must be provided to each subject [21 CFR 50.25]:

a) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
b) A description of any reasonably foreseeable risks or discomforts to the subject.
c) A description of any benefits to the subject or to others which may reasonably be expected from the research.
d) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.
e) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records.
f) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
g) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
h) A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

You failed to obtain legally effective informed consent from subjects to whom you administered the investigational new drug, (b) (4). You told the FDA investigator that you obtained informed consent from 22 subjects to whom you administered (b) (4); however, the documents that you provided as documentation of informed consent to the FDA investigator merely stated "I hereby authorize any and all treatment with FDA regulated device(s) for the treatment of my medical condition(s) and I hereby authorize payment to be made directly to the treating Health Practitioner". Those documents are inadequate in that they do not contain the required elements described above and are not specific to the investigational drug product administered. In addition, FDA regulations at 21 CFR 312.66 require that the investigator comply with the requirements in 21 CFR part 56 by using an informed consent document approved by an IRB that contains the information delineated in 21 CFR 50.25. You did not comply with this requirement, nor the protocol for

this trial which required that the informed consent form be approved in writing by the IRB. We note that the informed consent documents you provided to subjects were not approved by an IRB.

Your written response and attachments did not address this violation. While the attachments did include a copy of an informed consent form specific to (b) (4), they did not include any documentation indicating that this form was approved by an IRB nor signed by any of the subjects to whom you administered the investigational new drug, (b) (4).

4) **You failed to assure that an IRB complying with requirements set forth in 21 CFR Part 56 was responsible for the initial and continuing review and approval of a clinical study [21 CFR 56.103, 312.60, and 312.66].**

FDA regulations require that clinical investigations conducted under an IND (i.e. those subject to 21 CFR part 312) not be initiated unless that investigation has been reviewed and approved by an IRB meeting the requirements of 21 CFR part 56 [see 21 CFR 56.103]). Clinical investigators are responsible for assuring that an IRB conducts initial and continuing reviews of clinical investigations [21 CFR 312.66]. You violated these requirements by administering the investigational new drug, (b) (4), to subjects without obtaining IRB approval. You admitted to the FDA investigator that an IRB had not approved the study. However, without IRB approval you initiated the investigation and proceeded to administer the investigational new drug (b) (4) to subjects.

Your written response and attachments did not address this violation. The attachments you sent did include a letter from (b) (4) IRB stating that toxicity studies (b) (4) were approved. This letter is dated February 15, 2008. You administered the investigational product to subjects without IRB approval in January of 2007.

5) **You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual [21 CFR 312.62(b)].**

FDA regulations require you to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug [21 CFR 312.62(b)]. In addition, the protocol for the clinical investigation, in its Investigator Obligations section, specified that the investigator is expected to comply with applicable governmental regulations, and particularly emphasized maintaining independent case histories, supply accountability, and record retention. Under the protocol, the investigator is responsible for accurate and complete recording of all therapeutic data on the electronic case report forms. The protocol also states that separate and independent records of the patient's data must be maintained at all times. The Clinical Monitoring section of the protocol specified that during the course of the study the investigator will maintain source documents, such as product infusion records, laboratory reports, radiograms, consultation reports, history and physical examination reports, etc., for possible correlation and review.

You failed to maintain adequate and accurate case histories, including source documents and case report forms for subjects to whom you administered the investigational new drug, (b) (4) . You told the FDA investigator that you did not maintain any true case histories, just some dictated notes for subjects to whom you administered (b) (4) . You provided the FDA investigator with notes for only 10 out of 22 subjects. The notes you provided to the FDA investigator fail to meet the requirements of 21 CFR 312.62(b) and indicate that the study was not performed according to the investigational plan. In addition, the dates when the notes were prepared cannot be determined. Examples include, but are not limited, to the following:

a) For subject (b) (6) (b) (6), the notes have a date of January 8, 2007, but contain information to indicate that the subject received the second injection on January 19, 2007, the third injection on February 5, 2007, and the fourth injection on February 23, 2007.
b) For subject (b) (6) (b) (6), the notes have a date of January 8, 2007, but contain information to indicate that the subject received the second injection on January 22, 2007, the third injection on January 29, 2007, and the fourth injection on February 12, 2007.
c) For subject 1916, the notes have a date of January 15, 2007, but contain information to indicate that the subject received the second injection on January 16, 2007 and the third injection on January 18, 2007.
d) For subject (b) (6) (b) (6), the notes have a date of February 26, 2007, but contain information to indicate that the subject received the second injection on February 27, 2007 and third injection on February 28, 2007.
e) For subject (b) (6) (b) (6), the notes have a date of March 12, 2007, but contain information to indicate that the subject received the second injection on March 13, 2007 and the third injection on March 14, 2007.
f) For subject (b) (6) (b) (6), the notes have a date of January 24, 2007, but contain information to indicate that the subject received the second injection on January 30, 2007, the third injection on February 06, 2007, the fourth injection on February 13, 2007, the fifth injection on February 20, 2007, the sixth injection on March 1, 2007, and the seventh injection on March 14, 2007.

Your written response and attachments did not address this violation.

6) You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].

FDA regulations require that an investigator maintain adequate records of the disposition of the investigational drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)]. In addition, the protocol for the clinical investigation specified that the investigator is expected to comply with applicable governmental regulations, and contained particular emphasis on maintaining drug supply accountability. FDA's inspection found inadequate documentation for the receipt, dispensing, and reconciling of the investigational drug. The drug accountability records were inadequate to reconcile the dates of administration and

quantity of drug administered to each subject. Examples include, but are not limited to, the following:

a) For subjects (b) (6) (b) (6) (b) (6) (b) (6) (b) (6) (b) (6) (b) (6) (b) (6) the notes do not indicate the quantity of the investigational drug that was administered.
b) For subjects (b) (6) (b) (6) (b) (6) (b) (6) (b) (6), the notes do not indicate the dates or quantity of the investigational drug administered.

Your written response and attachments did not address this violation.

7) **You failed to conduct the clinical investigation according to the signed investigator statement and investigational plan, and to fulfill other responsibilities of an investigator, including to protect the rights, safety, and welfare of subjects under your care, as required by 21 CFR 312.40(a)(2), 312.60, and 312.66.**

When you signed the investigator statement (Form FDA 1572) for the above referenced clinical investigation, you agreed to take on the responsibilities of a clinical investigator. Each investigator using an investigational new drug in a clinical investigation must conduct his investigation in compliance with the requirements of Parts 50 and 56 [21 CFR 312.60, 312.40(a)(2), and 312.66]. Your general responsibilities as a clinical investigator (21 CFR 312.60) include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety and welfare of subjects under your care; and for the control of drugs under investigation. Our investigation indicates that you have failed to meet all of these responsibilities as outlined in items 1-6 above. These violations resulted in a failure to protect the rights, safety, and welfare of the subjects under your care.

Your written response and attachments did not address this violation.

Your response is unacceptable because it does not adequately address the violations set forth in the NIDPOE letter.

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 Eugene R. Leger, Acting Director, Division of Compliance Management and Operations (HFC-210), ORA Office of Enforcement, 15800 Crabbs Branch, Rockville, MD 20855, Telephone (240) 632-6868, FAX (240) 632-6859. 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.

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 had 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 Mr. Leger within the time period specified above and send a written response 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 to enter into a consent agreement, attached to the NIDPOE dated March 31, 2008, 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 investigational new drugs. 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 Mr. Leger within ten (10) business days of whether you wish to request a hearing or to have this matter resolved by consent agreement or information available to FDA.

Sincerely,

/s/

Michael Chappell
Acting Associate Commissioner
for Regulatory Affairs

Enclosures:
21 CFR part 10, subpart C
21 CFR part 16
21 CFR 312.70