DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

WARNING LETTER

VIA FEDERAL EXPRESS

NOV 13 2008

Fred Lam, M.D.
President
American Association of Acupuncture and Bio-Energetic Medicine
C/O Institute of Bio-Energetic Medicine
100 N. Beretania Street, Suite #208
Honolulu, HI 96817

Dear Dr. Lam:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB) from June 24 through July 15, 2008, by an investigator from the FDA San Francisco District Office. The purpose of this inspection was to determine whether your IRB is in compliance with applicable federal regulations. IRBs that review investigations of devices must comply with applicable provisions of Title 21, Code of Federal Regulations (21 CFR) Part 56-Institutional Review Boards, Part 50-Protection of Human Subjects, and Part 812-Investigational Device Exemptions. This letter also requests prompt corrective action to address the violations cited and discusses your written response dated July 29, 2008, to the noted violations.

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 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 several serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 50 -- Protection of Human Subjects, and Part 56 -- Institutional Review Boards. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 to Craig T. Twentyman, Ph.D., Co-Chairman for his review and discussed the observations listed on the form with him. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report is discussed below:

1. **Failure to determine that research involving children as subjects is in compliance with 21 CFR 50 Subpart D [21 CFR 56.111(c)].**

The IRB reviewed studies that included children's participation but failed to determine and document compliance with 21 CFR 50 Subpart D. Examples of this failure include, but are not limited to, the following studies:

a. (b)(4) study, "(b)(4) (b)(4) "
b. (b)(4) study, "(b)(4) and (b)(4) (b)(4) "

2. **Failure to prepare, maintain, and follow written procedures for conducting initial and continuing review of research [21 CFR 56.108(a) and 21 CFR 56.115(a)(6), 21 CFR 812.62 and 21 CFR 812.66].**

In order to fulfill the requirements of Part 56, each IRB shall prepare, maintain, and follow written procedures for conducting its initial and continuing review of research. Furthermore, according to 812.2(b)(1)(ii), abbreviated IDE requirements for studies of non-significant risk studies (NSR), a sponsor must submit an explanation as to why its device is a NSR device. The IRB is required to review and approve, require modifications in, or disapprove all investigations covered by these regulations. If an IRB determines that an investigation, presented for approval under 812.2(b)(1)(ii), involves a significant risk (SR) device, it shall notify the investigator and where appropriate, the sponsor (21 CFR 812.66).

Examples of this failure include, but are not limited to, the following:

a. Your IRB has no written procedure for determining the risk of each device. Your (b)(4) appears to imply that all (b)(4) devices are NSR devices. A blanket statement does not fulfill the regulatory requirements that are noted above since risk determination is not solely related to the type of device but is made in accordance with the indication for use of the device and how the device is used in a particular study. Therefore, you could theoretically have one type of device that is NSR in one study but SR in another.
b. (b)(4) study "(b)(4) (b)(4) " was approved on September 10, 2007, even though it did not list a title, a sponsor, results of previous research, subject selection, exclusion criteria, and provisions for managing adverse effects. All these are initial review requirements as described by your written procedures.

3. **Failure to conduct continuing review of research [21 CFR 56.109(f)].**

An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year. Examples of this failure include, but are not limited to, the following:

a. Your records indicate that a progress report for (b)(4) study,

"(b)(4)," has not been submitted within the last year. Your January 24, 2008, correspondence requesting the report went unanswered and your subsequent correspondence was approximately three months later, on May 3, 2008. That correspondence went unanswered as well. At the time of the inspection, you had taken no further action to address this.

b. Your records indicate that (b)(4) study, "(b)(4) (b)(4) (b)(4)" was approved by your IRB on September 6, 2004. Your records contain a copy of the informed consent and a January 13, 2005, letter requesting the annual report. Your IRB does not have on file copies of the protocol, progress reports, or evidence of continuing review for this study; nor do you have documentation that the study was terminated.

4. **Failure to require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25 [21 CFR 50.25 (a)(1) and 21 CFR 50.25 (a)(4), 21 CFR 56.109(b)].**

The IRB failed to ensure that informed consent documents contain all the information required by 21 CFR 50.25 such as 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 and a disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. Examples of this failure include, but are not limited to, the following:

a. The informed consent for (b)(4) study "(b)(4) (b)(4)," does not include a description of the procedures to be followed. Specifically, it does not address the (b)(4) that is required by the study protocol.

b. There was no disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject, in the informed consent, for the following studies:

   1. (b)(4) study "(b)(4) (b)(4)."
   2. (b)(4) study, "(b)(4) (b)(4)."

5. **Failure to prepare and maintain adequate documentation of IRB activities including copies of all research proposals reviewed, approved sample consent documents, and progress reports submitted by investigators [21 CFR 56.115(a)(1)]; and, failure to maintain minutes of IRB meetings, including attendance at the meetings, actions taken by the IRB, the vote on these actions including the number of members voting for, against, and abstaining, the basis for requiring changes in or disapproving research, and a written summary of the**

discussion of controverted issues and their resolution [21 CFR 56.115(a)(2)].

Examples of this failure include, but are not limited to, the following:

a. Your correspondence records indicate that on September 22, 2006, your IRB approved a study by (b)(4) involving a (b)(4) (b)(4); however, there are no meeting minutes on file to document that the IRB reviewed or approved the study. Also your IRB does not have on file copies of the protocol, consent form, progress reports, or evidence of continuing review for this study.
b. Your records indicate that on March 17, 2007, your IRB approved a change in protocol for (b)(4) study, "(b)(4) (b)(4)." Your IRB did not maintain, on file, a copy of the updated protocol for this study.
c. Your correspondence records indicate that on January 18, 2008, your IRB approved (b)(4) study, "(b)(4) (b)(4)," however, there are no meeting minutes on file to document that the IRB reviewed or approved the study.
d. There were no minutes for the April 27, 2005, and April 30, 2006, meetings.

The violations described above are not intended to be an all inclusive list of problems that may exist at the IRB. The IRB is responsible for ensuring compliance with the Act and applicable regulations.

In your response letter to the form FDA 483 addressed to Ms. Cassens and Ms. Yamane, you list specific actions you have taken to correct the examples listed in the observation section of this form. Your response is inadequate in that it does not provide substantive corrective actions or any preventative actions to avoid recurrence of the violations (i.e. development of standard operating procedures (SOPs), policies, or other means that would ensure compliance with the regulations). This appears to be an on-going problem as several of these citations are repeat violations dating as far back as 1997. They were also documented in your 2003 inspection in which, you received a form FDA 483.

Please note that a list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations is required, 21 CFR 56.115(a)(5). It is still unclear from the roster you provided in your response which members are "scientific" or "non-scientific" and which members are "affiliated" or "not affiliated" with the institution.

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. Any submitted corrective action plan must include copies of any SOPs, or policies that were developed; training attended or that will be attended. This documentation should also include completion dates or projected completion dates. Failure to respond to this letter and take appropriate

corrective action could result in the FDA taking regulatory action without further notice to you. Send your response to:

Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, Division of Bioresearch Monitoring, HFZ-311
9200 Corporate Boulevard, Rockville, Maryland 20850.
Attention: Ms. Doreen Kezer, Chief, Special Investigations Branch.

A copy of this letter has been sent to the San Francisco District Office, 1431 Harbor Bay Parkway, Alameda, CA 94502. Please send a copy of your response to that office.

If you have any questions, please contact Ms. Doreen Kezer at 240-276-0125, or at Doreen.Kezer@fda.hhs.gov.

Sincerely yours,

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