DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

NOV 14 2013

Institutional Review Board – Restrictions Imposed

By Certified Mail – Return Receipt Requested

Ref: CTS # EC120230/E001

Fred Lam, M.D.
President
American Association of Acupuncture and Bio-Energetic Medicine (AAABEM)
c/o Institute of Bio-Energetic Medicine
100 N. Beretania St.
Suite #208,
Honolulu, HI 96817

Dear Dr. Lam:

This letter imposing restrictions (IRB Restrictions Letter) informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection of the American Association of Acupuncture and Bio-Energetic Medicine (AAABEM) Institutional Review Board (IRB), which was conducted from December 19, 2012, to February 8, 2013, by an investigator from the FDA San Francisco District Office.[1] This re-inspection was conducted to determine whether the IRB is in compliance with applicable federal regulations, and to assess whether the IRB has implemented corrective actions following FDA Warning Letters of November 13, 2008, and March 24, 2011. IRBs that review investigations of devices must comply with applicable provisions of Title 21, Code of Federal Regulations (CFR) Part 56 - Institutional Review Boards, Part 50 - Protection of Human Subjects, and Part 812 - Investigational Device Exemptions (IDE).

At the close of the inspection, the FDA investigator presented an inspectional observations Form FDA 483 and discussed the observations listed on the form with Dr. Dee Alex Duarte, IRB Chairperson. We acknowledge receipt of the IRB's written response to the Form FDA 483 on March 5, 2013. We have reviewed the inspection report, the Form FDA 483, and your response. The IRB's written response is unacceptable, as explained below. This IRB

[1] The IRB also was inspected from January 22, 1997 to January 31, 1997, October 7, 2003 to October 16, 2003, June 24, 2008 to July 15, 2008, and October 25, 2010 to November 5, 2010. The IRB received Form FDA 483s after each of these inspections.

Restrictions Letter provides you with written notice describing AAABEM IRB's noncompliance with (violations of) applicable federal regulations governing the operation and responsibilities of IRBs under 21 CFR Part 56. The AAABEM IRB is required to respond in writing to FDA's Center for Devices and Radiological Health (CDRH) with a description of the corrective actions that will be taken by the IRB to achieve compliance with FDA regulations (21 CFR 56.120(a)). The name and address of the person that you should submit your corrective action plan to is provided at the end of the letter. A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. Failure to conduct continuing review of research at least annually. [21 CFR 56.109(f)]

An IRB is responsible for conducting continuing review of FDA-regulated research at intervals appropriate to the degree of risk, but not less than once per year. 21 CFR 56.109(f). The IRB failed to conduct continuing review of (b)(4) and (b)(4) research protocols. Specifically, the IRB initially met and reviewed the studies on September 18, 2011, and approved both protocols in letters dated October 18, 2011. The IRB neither reviewed nor approved the studies again before they expired on October 18, 2012. Nevertheless, study activity continued beyond that date.

The failure to conduct continuing review at least annually delays or prevents the IRB from considering any changes in the research or research-related events. Continuing review is required to ensure that appropriate human subject protection measures are in place throughout a study's duration.

This non-compliance by the IRB is a repeat violation. The 2008 inspection revealed instances where the IRB failed to conduct continuing review for different protocols. In the 2008 Warning Letter, FDA informed the IRB that continuing review of research must be conducted at least annually.

The IRB's 483 response states that on-time continuing review of research will be ensured by: (1) hiring an IRB secretary, (2) conducting continuing review at every meeting in the future, and (3) adopting a comprehensive continuing review procedure and risk evaluation scale. This response is inadequate because it fails to provide any assurances that the IRB will follow through on these commitments to remedy this repeat violation. The response failed to include:

- documentation that a secretary has been hired or documentation of efforts to hire a secretary;
- a copy of a schedule of meetings that will allow the IRB to conduct timely continuing review of protocols under its purview (conducting continuing review at all convened meetings will remedy the violation only if the meetings are appropriately scheduled to ensure that all research is reviewed at least annually);

- further explanation regarding what the "comprehensive continuing review procedure and a risk evaluation scale" will entail; and
- documentation of training IRB members and staff regarding these revisions.

In addition, because the IRB did not conduct continuing review of (b)(4) research, the IRB did not address her September 20, 2012, request to enroll (b)(4). It is important to review requests for study changes because an IRB must review and approve protocol changes, amendments, and informed consent documents (ICD) as a component of human subject protection. We suggest that the IRB direct particular attention to all requested changes in research protocols and any accompanying materials in a timely manner and inform the clinical investigator of the outcome.

Even when the IRB did conduct timely continuing review, its review was inadequate. For example, during its review of the protocol titled "(b)(4)" in January 2013, the IRB failed to recognize that the study was intended to run only (b)(4) years and end in January 2010. The IRB, therefore, did not notify the clinical investigator that the study had expired. Protocol designs include timeframes for the research to ensure that an adequate number of subjects are exposed to experimental treatment without imposing undue risk on subjects. Extending the timeframe for the research may not only increase risk to subjects if the experiment is not beneficial, but may also delay access to new treatments.

2. Failure to review proposed research at convened meetings. [21 CFR 56.108(c)]

Except when an expedited review procedure is used, the IRB must review proposed research at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. 21 CFR 56.108(c). The IRB failed to adhere to these requirements. Specifically, there is no evidence that the proposed (b)(4) research of (b)(4) was reviewed at a convened meeting of the IRB. The document entitled "(b)(4)" does not reflect that a convened meeting was held and the document itself is an unacceptable substitute for a convened meeting.

The failure of the IRB to review proposed research at a convened meeting is a serious violation. IRB review of proposed research is conducted at convened meetings so all members of the committee have an opportunity to discuss all the risks and benefits of the research experiment in order to ensure that human subjects are adequately protected. Failure to do so can place subjects at increased risk of harm.

In its 483 response, the IRB states that, to prevent this problem from arising again, all voting on new applicants and studies will be conducted at convened meetings of the IRB, and Dr. Duarte will recommend to the IRB that this statement be added to the IRB's SOPs. This response is inadequate. The IRB Protocol (page 3) already describes the process for continuing review, and the Protocol (page 4) also already defines criteria for attendance at convened meetings. No assurance has been provided by the IRB that it will comply with these requirements if they appear in its SOPs when it has failed to comply with similar provisions appearing in its Protocol.

We also identified the following issue during our review of the documents that were collected during the inspection. Although the item below was not included on the Form FDA 483, it is important that this deficiency is corrected.

3. Failure to ensure that ICDs include all of the elements set forth in 21 CFR 50.25 and failure to follow written procedures for initial review and continuing review. [21 CFR 56.109(b)]

An IRB shall require that information given to subjects as part of informed consent is in accordance with 21 CFR 50.25. Section 50.25(a)(5) requires that informed consent include "[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." The IRB Protocol (page 14) sets forth identical requirements. The IRB failed to comply with 21 CFR 50.25 and its written procedures.

Specifically, for at least two studies, the IRB approved ICDs that did not include a statement (1) describing the extent, if any, to which confidentiality of records identifying the subject will be maintained or (2) noting the possibility that FDA may inspect the records, as required by 21 CFR 50.25(a)(5). Examples of such documents include, but are not limited to ICDs for:

- [redacted] (b)(4): Consent to Participate as a Subject in an Investigational Study: (b)(4) [redacted]
- [redacted] (b)(4): Consent to Participate as a Subject in an Investigational Study: (b)(4) [redacted].

Please describe in detail the measures that the IRB will take to prevent any recurrence going forward.

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

Based on the continuing pattern of deficiencies found during inspections of your IRB, AAABEM IRB does not meet the requirements of 21 CFR Part 56. We have no assurance that the IRB procedures are adequately protecting the rights and welfare of the human subjects involved in research. For this reason, and the reasons described elsewhere in this letter, effective immediately, FDA is placing on the IRB the following two restrictions:

1. **Withholding approval of new studies subject to the requirements of Part 56 that are reviewed by the IRB. (21 CFR 56.120(b)(1)).**

2. **Terminating ongoing studies subject to Part 56, when doing so would not endanger the subjects. (21 CFR 56.120(b)(3)).**

Because FDA is withholding approval of new studies subject to Part 56 that are reviewed by the IRB, a sponsor may not begin any new clinical investigation of a device, either significant or non-significant risk, subject to 21 CFR Part 812, and which is not exempt under 21 CFR 812.2(c). Please notify all affected sponsors and clinical investigators of the restriction.

Moreover, FDA is terminating all ongoing studies subject to Part 56 when doing so would not endanger the subjects. Based on information collected to date, FDA does not believe termination of any of the ongoing studies that you review would endanger subjects. If the IRB or any sponsor believes that termination would endanger subjects, FDA should be notified. Please notify the affected sponsors and clinical investigators of any termination.

These restrictions will remain in effect until such time as FDA has evidence of adequate corrective activities and notifies you in writing that the IRB's corrective actions are satisfactory. These restrictions do not relieve the IRB of its responsibilities to receive and respond to reports of unanticipated problems and unanticipated adverse device effects, and routine progress reports from ongoing studies.

Within 30 working days of receiving this letter, you should respond in writing with a description of the corrective actions that will be taken or that have been implemented to bring the IRB into full compliance with FDA regulations.

Your response should address each item of noncompliance listed above. If you do not believe that your IRB is in violation of FDA requirements, include your reasoning and any supporting information for our consideration. If you assert that full and adequate correction has been achieved, you should include any

documentation necessary that affirms your corrective actions. For each action to be accomplished, include the projected completion dates.

Include with your response a copy of the IRB's written communication to each of the affected sponsors and clinical investigators, notifying them of the current FDA-imposed restrictions. In addition, please provide a list of all studies being reviewed by your IRB that are subject to 21 CFR Part 56, and a list of all studies that are affected by the above restrictions.

Your failure to adequately respond to this letter may result in further agency action, including action under 21 CFR 56.120 and 56.121.

Your response should reference "CTS # EC120230/E001 and be sent to:

Attention: Linda Godfrey
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3448
Silver Spring, Maryland 20993-0002.

CDRH will carefully consider your written response. Additionally, your corrective actions will be verified during a future inspection.

Sincerely yours,

Steven D. Silverman
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:

Dee Alex Duarte, OD
IRB Chair
American Association of Acupuncture and Bio-Energetic Medicine
92-104 Waialii Pl.
Unit O-1202
Kapolei, HI 96707