Institutional Review Board - Restrictions Imposed

VIA UNITED PARCEL SERVICE

July 10, 2017

Dean R. Bonlie, DDS, Custodian of Records
Advanced Magnetic Research Institute, Institutional Review Board
6230 E Tropical Pkwy
Las Vegas, NV 89115

Dear Dr. Bonlie:

This letter imposing restrictions (IRB Restrictions Letter) informs you of objectionable conditions observed during the U.S. Food and Drug Administration (FDA) inspection of Advanced Magnetic Research Institute (AMRI) Institutional Review Board (IRB) from October 24, 2016 to October 25, 2016, by an investigator from the FDA San Francisco District Office. This was an initial inspection of the AMRI IRB conducted at the same time as a follow-up inspection of AMRI-International, LLC, the sponsor of all of the studies reviewed by the AMRI IRB. In 2013-14, the sponsor was inspected, issued a FDA Form 483, and issued a warning letter (addressed to you, as president of the sponsor) for various deficiencies including several relating to the AMRI IRB. This inspection was conducted, in part, to determine whether the 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 (CFR) Part 56 - Institutional Review Boards, Part 50 - Protection of Human Subjects, and Part 812 - Investigational Device Exemptions.

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 you. We have reviewed the inspection report and the Form FDA 483, as explained below. We note that despite agreeing to do so in the inspection close-out discussion, you have not responded to the observations contained in that report and have not acknowledged any corrective actions to address those observations.

This IRB Restrictions Letter provides you with written notice describing AMRI IRB's noncompliance with (violations of) applicable federal regulations governing the operation and responsibilities of IRBs under 21 CFR Part 56. AMRI 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 (or have been) 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 prepare, maintain, and follow written procedures governing the functions and operations of the IRB. [21 CFR 56.108(a), 56.108(b), and 56.115(a)(6)].**

In order to fulfill the requirements of Part 56, each IRB must prepare, maintain, and follow written procedures describing IRB functions and operations as specified in the regulations.

Your IRB failed to fulfill these requirements. Specifically, the IRB did not prepare, maintain, and follow written procedures for the following required IRB activities:

- Conducting initial and continuing review of research and for reporting IRB findings and actions to the investigator and the institution
- Determining which projects require review more often than annually and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review
- Ensuring prompt reporting to the IRB of changes in research activity
- Ensuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects
- Ensuring prompt reporting to the IRB, appropriate institutional officials, and FDA of:
    a) Any unanticipated problems involving risks to human subjects or others.
    b) Any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of the IRB.
    c) Any suspension or termination of IRB approval.

During the inspection close-out discussion, you acknowledged that the IRB had not prepared and maintained *any* written procedures.

Written procedures are a critical, fundamental component to the IRB's overall operations. Written procedures are important because they describe how an IRB operates and conducts its major functions to help ensure the protection of human subjects participating in clinical research. Written procedures also help to ensure that research is reviewed in a timely manner and that the findings are adequately reported to the institution and the clinical investigator. Compliance with these requirements is intended to protect the rights and welfare of research subjects involved in such investigations. Hence, it is imperative that the IRB prepare, maintain, and follow written procedures for its operations. The lack of written procedures for the review of research may have an adverse impact on the rights, safety, and welfare of research subjects and decrease the integrity and validity of research data.

Please provide an explanation of the actions that the IRB has taken or plans to take to ensure that the IRB prepares, maintains, and follows written procedures. The response should provide documents relating to proposed and completed actions, such as standard operating procedures (SOP), a list of staff trained on those procedures, as well as dates trained.

2. **Failure to prepare and maintain adequate documentation of IRB activities including copies of correspondence between the IRB and the investigators and a list of IRB members, along with their qualifications. [21 CFR 56.115(a)(4) and 56.115(a)(5)]**

An IRB shall prepare and maintain adequate documentation of IRB activities including copies of correspondence between the IRB and the investigators. Additionally, an IRB is required to prepare and maintain a list of IRB members identified by name, earned degrees, representative capacity, indications of experience, and any employment or other relationship between each member and the institution. The records required by this regulation shall be retained for at least three years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the FDA at reasonable times and in a reasonable manner (21 CFR 56.115(b)).

Your IRB failed to prepare and maintain correspondence between the IRB and investigators. During the inspection close-out discussion, you acknowledged that correspondence between the IRB and clinical investigators was not maintained by the IRB. The IRB also failed to prepare and maintain a list of IRB members and their qualifications from 1999-2004 and in 2008.

It is critical that the IRB prepare and maintain adequate documentation of IRB activities in order to ensure that the rights and welfare of study subjects are protected. An updated member list showing the relationship between each member and the institution is also important to ensure that the IRB's review of research is fair and equitable. It would also help to prevent the participation of any member who may have a conflict of interest (21 CFR 56.107(e)).

In addition, it is important that the IRB maintain copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, reports of injuries to subjects, and records of continuing review activities, such as IRB continuing review approval letters. By doing so, the IRB ensures that sponsors and clinical sites are aware of the IRB requirements for various activities, such as knowing when to start enrolling subjects, report adverse events, etc.

Please provide an explanation of the actions the IRB has taken or plans to take to ensure that the IRB prepares and maintains adequate documentation of IRB activities. Your response should provide documents relating to proposed and completed actions, such as any relevant SOPs, a list of staff trained on those procedures, as well as dates trained.

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

The IRB must ensure that the basic elements of informed consent, and any additional elements when appropriate, are provided to each subject as described in 21 CFR 50.25.

Your IRB failed to adhere to these requirements. Specifically, the informed consent documents (ICD) for the general pilot (phase 2) study, entitled “Protocol for Patient Evaluation Using Magnetic Molecular Energizer,” did not adequately address the basic elements of informed consent as described in 21 CFR 50.25(a). For example, the ICDs did not include:

- A description of any reasonably foreseeable risks or discomforts to the subject – for example, there is no mention in the ICDs of the subjects experiencing nausea, which has been described by the sponsor and clinical investigators as a risk from the device in published literature.
- A description of any benefits to the subject or to others which may reasonably be expected from the research – we note that the ICDs state that there may or may not be benefits, but there is no description as to what those potential benefits may be.
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

We also note that the ICDs do not meet the regulatory requirements of 21 CFR 50.20, which prohibits the use of exculpatory language through which the subject or representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, sponsor, the institution, or its agents from liability for negligence. Specifically, the "Special Consent for Therapy and Treatment" form that was used included the following statement: "In addition, I agree not to hold my physician, staff of the clinic appointed by this physician as legally responsible for any complications solely related to the administration of this treatment."

A valid informed consent process ensures that research subjects have a clear understanding of risks of participation in a research protocol, have sufficient opportunity to consider whether to participate in the study, and make an informed decision if they decide to participate.

The elements omitted from the ICDs include important information such as foreseeable risks and benefits of participating in the study and alternative treatment options for their medical condition. Study subjects are required to have this information in order to make an informed decision about participating in clinical research.

Please provide an explanation of the actions that your IRB has taken or plans to take to ensure that ICDs that you review and approve include the information required by 21 CFR 50.25. Your response should provide documents relating to the proposed and completed actions, such as any revised informed consent documents, revised SOPs, a list of staff trained on the execution of any new documents and procedures, as well as dates trained.

4. **Having members participate in the initial/continuing review of any project in which the member has a conflicting interest. [21 CFR 56.107(e)]**

No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflict of interest, except to provide information requested by the IRB (21 CFR 56.107(e)). The IRB failed to adhere to these requirements. For example, minutes from the 2000, 2001, 2002, and 2003 IRB meetings show that you took part in the IRB's review and voted on various studies for which you were the sponsor, including the general pilot (phase 2) and diabetic neuropathy pivotal (phase 3) studies. Additionally, based on the limited records available at inspection, it appears that various IRB members voted on studies for which they were clinical investigators at the time of the vote or subsequently.

These appear to be significant conflicts of interest that should have been recognized and addressed by the IRB. The IRB's failure to ensure that voting IRB members did not have conflicts of interest has lessened the likelihood of a fair and equitable IRB review of the study. As a result, the safety and welfare of human subjects may have been jeopardized and adequate human subject protection measures may not have been implemented.

Please provide an explanation of the actions the IRB has taken or plans to take to ensure that the IRB will not allow members with conflicts of interest to vote. The response should provide documents relating to proposed and completed actions, such as any relevant SOPs, a list of staff trained on those procedures, as well as dates trained.

5. **Failure to register. [21 CFR 56.106]**

Each IRB in the United States that reviews clinical investigations regulated by FDA under sections 505(i) or 520(g) of the Federal, Food, Drug, and Cosmetic Act (the Act), and each IRB in the United States that reviews clinical investigations that are 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 (HHS) (21 CFR 56.106(a)). The initial registration must occur before the IRB begins to review such a clinical investigation and must be renewed by the IRB every three years (21 CFR 56.106(c)).

Your IRB failed to register before beginning review of clinical investigations. Although these issues were discussed with you during the IRB inspection, the IRB has still not registered.

IRBs play an integral role in ensuring that clinical studies are conducted in accordance with FDA regulations that provide protections for the rights and welfare of human subjects and that help to ensure the quality and integrity of the data submitted in support of marketing applications. The registration system enables FDA to identify those IRBs reviewing clinical investigations regulated by FDA. The registration system also enables FDA to share, in a timely fashion, educational and other information with IRBs, including information about adverse reactions that may be attributed to a particular product, new regulatory requirements and policies that relate to human subject protection and data integrity, and problems with a particular protocol or clinical investigator. Please provide an explanation of the actions that the IRB has taken or plans to take to ensure compliance with these requirements.

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

Based on the serious deficiencies found during this inspection, your IRB does not meet the requirements of 21 CFR Part 56. We have no assurance that your IRB's 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 the following two restrictions on your IRB:

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 your 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 studies, including suspended studies, that you review would endanger subjects. If your IRB or any sponsor believes that termination would endanger subjects, FDA should be notified to discuss. Please notify the affected sponsors and clinical investigators of any termination.

These restrictions will remain in effect until such time as FDA receives from you evidence of adequate corrective action and notifies you in writing that the corrective actions are adequate. These restrictions do not relieve your IRB of its responsibilities to receive and respond to reports of unanticipated problems and unanticipated adverse device effects, and routine progress reports from any 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 your 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 or artifacts that affirm your corrective actions. For each action to be accomplished, include the completion or projected completion date(s).

Include with your response a copy of your 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 the 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 further action under 21 CFR 56.120 or disqualification under 21 CFR 56.121.

Your response should reference "CTS # EC170009/E001" and be sent to:

Attention: Veronica Calvin, MA
Food and Drug Administration

Center for Devices and Radiological Health
Office of Compliance
Division of Bioresearch Monitoring
10903 New Hampshire Avenue
Building 66, Room 3508
Silver Spring, Maryland 20993-0002.

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

A copy of this letter has been sent to FDA's San Francisco District Office, 1431 Harbor Bay Pkwy, Alameda, CA 94502-7070. Please send a copy of your response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA-regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA-regulated device clinical research activities. These modules are located at the following website address: http://www.fda.gov/Training/CDRHLearn/.

If you have any questions, please contact Tamika Allen, RN, MSN at (301) 796-1164 or Tamika.Allen@fda.hhs.gov.

Sincerely yours,

Robin W. Newman

Digitally signed by Robin W. Newman
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