Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance
Bioresearch Monitoring Branch
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TO: Fred Fox, J.D., Chairman Emeritus, Executive Director
Biomedical Research Institute of America dba Biomed IRB

Facsimile Number: 619-282-9998

FROM: Mary Malarkey, Director, OCBQ

DATE: March 29, 2012

Please see the attached letter.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852-1448

March 29, 2012

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CBER-12-03

Warning Letter

Fred Fox, J.D., Chairman Emeritus, Executive Director
Biomedical Research Institute of America dba BioMed IRB
7676 Hazard Center Drive, Suite 500
San Diego, California 92108

Dear Mr. Fox:

This letter describes the results of the Food and Drug Administration (FDA) inspections of the BioMedical Research Institute of America, doing business as BioMed Institutional Review Board (hereafter referred to as "the IRB"), which were conducted from September 22 through October 25, 2010, and from August 8 through August 19, 2011. The first inspection focused on the IRB's review of selected studies for the sponsor [redacted] and was conducted by a Los Angeles District FDA investigator. Due to the nature of the deficiencies observed in the first inspection, a second inspection was conducted to provide a broader assessment of the IRB's operations. The second inspection was conducted by the same district FDA investigator accompanied by an inspector from the Center for Biologics Evaluation and Research (CBER). The FDA representative(s) conducted the inspections to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations published in the Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. The inspections were part of FDA's Bioresearch Monitoring Program, which includes inspections designed to review IRB operations for clinical studies using investigational products and for the protection of human subjects.

The focus of the first inspection was limited to the following studies:

- A Phase I/II Study of Polyclonally Activated, Intentionally Mis-Matched, Allogeneic Th1 Memory Cells ([redacted]) in Patients with Relapsed or Refractory Hematological Malignancy without Prior Conditioning (Protocol [redacted], hereinafter "Study 1"), and

- A Phase I/II Study of an experimental therapeutic cancer vaccine created in-situ in patients with refractory or metastatic cancer (Protocol [redacted], hereinafter "Study 2").

The focus of the follow-up inspection included meeting minutes, membership, and general review of research by the IRB.

The FDA investigator from the FDA Los Angeles District Office issued and discussed the Forms FDA 483, Inspectional Observations with you at the conclusion of each inspection. The FDA inspector from CBER participated by telephone at the close of the second inspection. We received and reviewed the IRB's responses to the Forms FDA 483, which were dated November 2, 2010, August 30, 2011, September 1, 2011, September 2, 2011, September 15, 2011, and January 12, 2012.

We have determined that the IRB significantly violated applicable federal regulations governing the operation and responsibilities of IRBs as published in Title 21, Code of Federal Regulations (CFR), Part 56 (available at http://www.access.gpo.gov/cgi-bin/cfrassemble.cgi?title=201021). The applicable provisions of the CFR are cited for each violation listed below.

1. The IRB failed to fulfill membership requirements. [21 CFR § 56.107].

A. The IRB did not possess the professional competence necessary to adequately review the specific research activities. For example:

i. On January 27, 2010, the IRB reviewed and approved a study involving subjects with unresectable stage III or stage IV melanoma. Review of the IRB's records indicates that the IRB lacked the professional competence necessary to review this study and determine whether it met the criteria for approval under 21 CFR § 56.111, including whether risks to subjects were "reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result." For example, the IRB did not include an individual with professional competence in oncology (e.g., a physician), nor is there any documentation to show that the IRB invited individuals with competence in this area to assist in the review of this study, as permitted by 21 CFR § 56.107(f).

ii. On July 7, 2010, the IRB reviewed and approved a study of subjects with type 1 diabetes. The IRB did not include an individual with professional competence in diabetes treatment (e.g., a physician), nor is there any documentation to show that the IRB invited individuals with competence in this area to assist in the review of this study, as permitted by 21 CFR § 56.107(f).

iii. On July 14, 2010, the IRB reviewed and approved a study involving subjects with non-small cell lung cancer. The IRB did not include an individual with professional competence in oncology (e.g., a physician), nor is there any documentation to show that the IRB invited individuals with competence in this area to assist in the review of this study, as permitted by 21 CFR § 56.107(f).

B. The IRB allowed non-members to vote.

i. IRB meeting minutes from April 20, 2011, and May 25, 2011, show that an attendee identified as "EE" participated in voting. According to the IRB membership rosters, EE was not a member of the IRB when these meetings were conducted.

ii. IRB meeting minutes from July 7, 2010, and July 14, 2010, show that an attendee identified as "DH" participated in voting. According to the IRB membership rosters, DH was not a member of the IRB when these meetings were conducted.

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

A. The IRB's written procedures are inadequate because they do not require the approval of a majority of those members present at the meeting for research to be approved by the IRB. Under 21 CFR § 56.108(c), in order for research to be approved by an IRB, it must receive "the approval of a majority of those members present at the meeting." However, the IRB's Standard Operating Procedure (SOP) 402, *Initial Review of Research,* (version 4.1 January 13, 2010), provides that:

> In the event of more than the required quorum of Primary voting members being present at an IRB meeting, only three members will be required to vote. *Which primary members will vote during the IRB meeting is at the discretion of the Chair.* (emphasis added).

Under this SOP, research could be deemed "approved" without the approval of a majority of those members present at the meeting. For example, if five primary Board members are present at an IRB meeting and the Chair limits voting to three members, research could be deemed approved by the IRB with just two approval votes; i.e., by a minority of the members present at the meeting.

Your September 1, 2011 letter responding to the Form 483 issued to you on August 30, 2011 ("September 1, 2011 response letter"), confirms that the IRB Chair "routinely limited voting" to three members regardless of the number of primary Board members who were present at the meeting. As shown in the table below, meeting minutes for at least 11 meetings indicate that the attendees who voted did not include one of the primary members in attendance at the meeting.

Meeting Date	Attendees with recorded vote or abstention ("alternate members" in bold)	Primary member in attendance with no recorded vote or abstention
04/20/2010	FF, **EP, PP**	JD
07/07/2010	FY, **JZ, DH**	FF
07/14/2010	FF, FY, **DH**	JD
08/11/2010	HHS, PS, **DH**	MK *NOTE: MK is the only physician member of the IRB; DH is a pharmacy student whose qualifications are not comparable.*
08/25/2010	HHS, PS, **DH**	MK *NOTE: MK is the only physician member of the IRB; DH is a pharmacy student whose qualifications are not comparable.*
09/01/2010	HHS, PS, **KW**	JD
09/08/2010	HHS, PS, **KM**	JD
09/15/2010	HHS,PS, MK, **CB, AM**	JD
11/03/2010	HHS PS, **EP**	CB
01/26/2011	MK, **JF, AM**	CB
02/23/2011	HHS, PS, MK	CB

In your September 1, 2011 response letter, you explain that the IRB Chair:

> ...can designate the voting quorum so that there is certainty in an effective quorum for the meeting, and, without that, the IRB meeting would be worthless. The chairman makes that designation in advance of voting or discussion, at the start of any IRB meeting, and the purpose is to safeguard that there will be a binding action voted at the meeting.

This explanation is not adequate because your written procedures would allow research to be approved by the IRB without the approval of a majority of those members present at the meeting.

B. The BioMed IRB's SOP 402, *Initial Review of Research* (version 4.1 January 13, 2010), states that pertinent study documentation is made available to the IRB voting members prior to and during the meeting. In addition, SOP 200 *Membership of the IRB,* (version 4.2 July 29, 2010) Item 7.H. states

> All IRB committee members attending the meeting, including those participating and / or voting via telephone conference, shall receive and review in advance at least the following research materials: (1) A Protocol Summary *written in sufficient detail to determine appropriateness of the study specific statements in the consent documents, including inclusion/ exclusion criteria* (2) Informed Consent Document.

The FDA inspection noted several instances where the materials described above were not distributed to all IRB members who attended the meeting. Examples include:

i. An IRB meeting "Memorandum" dated January 21, 2011, indicates that the materials for new studies on the agenda for the January 26, 2011, meeting were distributed to primary members HHS, PS, and KM, and alternate member AM. At this meeting, primary member MK and alternate member JF voted on the new studies but there is no documentation to show that they received the new study materials for review prior to the meeting or had adequate time during the meeting to review the new materials.

ii. An IRB meeting "Memorandum" for a meeting scheduled June 22, 2011, shows that materials for new studies were provided to three primary members HHS, PS, and MK, and alternate member RJ. The meeting minutes show that primary member KM, who did not receive the materials according to the "Memorandum," voted at the meeting. Member MK, a primary member who was present at the meeting and received the materials, was excluded from voting.

In your September 1, 2011, letter, you explain that meeting materials are sent to members who are likely to be available and that their availability may change. You state that your future plans include distributing materials in advance to all members electronically. However, you have not provided documentation to show that this proposed corrective action has been implemented.

3. **Minutes of IRB meetings are not sufficient to show 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)].**

A. The IRB's meeting minutes are not sufficient to show attendance at meetings because they often contain conflicting information concerning who attended the meeting. For example, as shown in the table below, for three meetings, a summary section of the minutes entitled "IRB Action View" ("Action View section") identified a different group of attendees than the body of the minutes.

Date of Meeting	Section of Minutes	Identified Individuals in Attendance
12/09/09	Action View	11, 22, 33, 4a, 4b, 4c, 5a, 5b, 5c, 5d
	Body	11, 33, 4a, 4c, 5c ,5d, 6e, 77, 88, 99
04/07/10	Action View	11, 22, 33, aa, bb, cc, dd, ee
	Body	11, 22, 33, 4a, 4c, 5d, 6e, 77, 88, 99
06/29/11	Action View	11, 22, 33, 44,1a, 1b, 1c, 1d
	Body	11, 22, 33, 44,1a, 1c, AA, AC, DD, 1A, 1C, 1D, PS

B. Minutes are not sufficient to show actions taken by the IRB and the vote on these actions including the number of members voting for, against, and abstaining.

i. The IRB had a practice of requiring each member present at a meeting to capture his/her own notes on what occurred at the meeting (or in some instances, a meeting "Observer" recorded a member's minutes). The IRB then assembled all of the notes from these multiple individuals into a single document to create minutes for the meeting. Additionally, the IRB often incorporated portions of minutes from previous meetings into the minutes of subsequent meetings. As a result, the minutes for any given meeting are often more than 150 pages long, and often do not accurately represent the actions of the IRB at that particular meeting. For example, the meeting minutes for April 7, 2010 indicate that, on that date, the IRB debated proposed protocol amendments to Study 2, and conditionally approved certain protocol amendments. However, comparison with minutes from earlier meetings indicates that the discussion and vote occurred four months earlier, on December 9, 2009.

ii. The meeting minutes for December 9, 2009, state that "a quorum of three members voted," but the "Summary of Votes" section documents only two votes.

iii. The meeting minutes for January 17, 2011, indicate that at least three voting members were present, but the "Summary of Votes" section documents only two votes.

iv. The meeting minutes for January 19, 2011, indicate that at least three voting members were present, but the "Summary of Votes" section documents a total of only two votes.

In your January 12, 2012 letter, as a corrective action you propose generating an additional "truncated yet still an official set of minutes" for FDA's review. Creating multiple versions of meeting minutes is not an acceptable corrective action. One set of minutes should be prepared for each IRB meeting, and the minutes must accurately represent the actions of the IRB at that particular meeting, including the number of members voting for, against, and abstaining from each action; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

v. Minutes are not sufficient to show a written summary of the resolution of controverted issues. For example, minutes from a meeting held on October 7, 2009, indicate that the IRB debated whether "it is a little too soon for the company to amend the protocol [for Study 2] to have the dosage so dramatically increased." The minutes also indicate that controversy was raised regarding the insurance payment: "a long conversation addresses the ethical question of price/payment in regards to how much is ethical to ask someone to pay." However, no written summary of the resolution of these controverted issues was included in the meeting minutes as required.

This letter is not intended to contain an all-inclusive list of deficiencies in the operations of the IRB. It is incumbent upon you and the IRB to correct the violations cited in this letter, and to conduct a thorough review of the IRB's SOPs and practices to ensure full compliance with the regulations.

Based on the deficiencies found during these two inspections, including deficiencies observed in the first inspection that were also found in the second inspection, we have no assurance that the IRB procedures are adequately protecting the rights and welfare of the human subjects of research. For this reason, in accordance with 21 CFR §§ 56.120(b)(1) and (2), and effective immediately,

- **FDA will withhold approval of all new studies subject to 21 CFR Part 56 and reviewed by the IRB; and**

- **No new subjects are to be enrolled in any ongoing studies subject to 21 CFR Part 56 and approved by the IRB.**

These restrictions will remain in effect until such time that you have received written notification from this office that adequate corrections have been made. These restrictions do not relieve the IRB of its responsibility for receiving and reacting to reports of unexpected and serious reactions and routine progress reports from ongoing studies.

You are to notify this office in writing, within fifteen (15) business days of receipt of this letter, of the specific actions you have taken or plan to take to bring the IRB into full compliance with FDA regulations. Your response should address each item listed above, and should include any documentation necessary to show that full and adequate correction has been achieved. Include the projected completion dates for each action to be accomplished.

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.

Your failure to respond to this letter, or to implement adequate corrective action, may result in further administrative actions, as authorized by 21 CFR §§ 56.120 and 56.121. These actions include, but are not limited to, the termination of ongoing studies subject to 21 CFR Part 56 and approved by your IRB, and the initiation of regulatory proceedings for disqualification of your IRB.

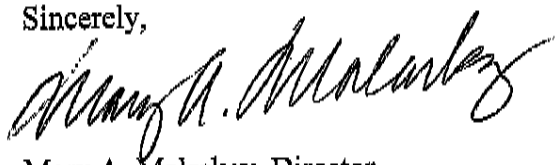
On the basis of your response, FDA may schedule a reinspection to confirm the adequacy of your corrective actions.

Please send your written response to:

Christine J. Drabick
Division of Inspections and Surveillance (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland, 20852-1448
Telephone: (301) 827-6336

We request that you send a copy of your response to the FDA District Office listed below.

Sincerely,



Mary A. Malarkey, Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

cc: Alonza Cruse, District Director, HFR-PA200
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