BioMed·IRB

Christine J. Drabick

Division of Inspections and Surveillance (HFM-664)

Office of Compliance and Biologics Quality

Center for Biologics Evaluation and Research

1401 Rockville, Maryland, 20852-1448

March 31, 2012

RE: Response to Warning Letter dated March 29, 2012

The purpose of this letter is to provide a formal response to warning letter dated March 29, 2012, and to notify the Office of Compliance and Biologics Quality of the specific actions taken and the actions we plan to take to bring BioMed IRB into full compliance with FDA regulations. The following response lists each violation cited in the warning letter, along with a response addressing each item. Within each item are footnotes that will also serve as the list of attachments/documentation to demonstrate our corrective action(s).

FDA Violation 1: "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:"*
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> *"i. On July 7, 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 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 they IRB invited individuals with competence in this area to assist in the review of this study, as permitted by 21 CFR § 56.107 (f)."*

IRB RESPONSE: The original review of the above referenced study ("Study 1") was voted on at an IRB March 11, 2009, where the scientific voting member present at that meeting, [redacted] has research experience in oncology, which "resulted in several papers and two patents as co-inventor"[i]. Notably, prior to protocol amendment v9 (meeting item referenced above in 1.A.i.), BioMed received requests by two independent physicians for a compassionate use exemption for [redacted] during the clinical hold that the FDA placed on the study article. These two physicians had evaluated the study objective and method and found the investigational product to be the best available option for their patients. Unfortunately, in these cases, the potential subjects were terminally ill and for whom any other self reported treatments had failed. In the evaluation of risks to be "reasonable in relation to anticipated benefits", the members voting at the January 27, 2010 meeting had received training based on the Belmont Report and Declaration of Helsinki.

> *" 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 § 56.1079(f)"*

IRB RESPONSE: In reference to the diabetes type 1 follow up study (no dosing) voted on by BioMed IRB on July 7, 2010, BioMed IRB believes that individuals qualified to review and approve the study were in attendance. Our scientific, unaffiliated member, who voted at that meeting, has a Ph.D. in molecular and medical pharmacology, and specializes in immunology. BioMed IRB aims to qualify voting members in compliance with 21 CFR Part 56.107 (c) "Each IRB shall include at least one member whose primary concerns are in the scientific area…" and 21 CFR Part 56.107(a)

> Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, cultural backgrounds, and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects.

Your letter states *"The IRB did not include an individual with professional competence in diabetes treatment (e.g., a physician)"*, however the regulations do not specify that the person knowledgeable in the area of the study to be reviewed must be a physician. According to [redacted]s resume, she was a "member of a cross functional team of biologists and chemists on several

compounds that have advanced into global Phase I/II trials for autoimmune and inflammatory indications"[ii] Your letter further states *"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)"*. The comments from the IRB staff member ("Observer") attending the July 7, 2010 meeting notes, "one of the observers is a pediatrician". [iii] This observer, [redacted] (herein also referred to as [redacted]), became a voting member of BioMed IRB on July 14, 2010; one week after the diabetes study was approved. [redacted] was present at this meeting as a knowledgeable person to assist in the review. As part of her clinical experience as a physician/pediatrician (the study in question had a pediatric population), she had "presented a seminar on 'Newer trends in management of Diabetes Mellitus' during a CME on Diabetology"[iv]

> *"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)."*

IRB RESPONSE: Your letter states that at the July 14, 2010 meeting, BioMed IRB did not have someone voting who had professional competence in oncology, or an individual to assist in the review as allowed by 21 CFR § 56.107(f). For this protocol, the chair and voting member, [redacted], has research experience in oncology, including projects that "resulted in several papers and two patents as co-inventor"[v]. Additionally, [redacted] attended the meeting but not as a voting member; one item on the agenda was a vote to add her to the roster. She participated in the discussion and clarification; she is "1c" in the code within the minutes. As noted in the previous response, she is a physician with clinical experience in internal medicine. Also attending, but not voting, was an alternate member who is a PharmD with knowledge in the area of oncology as vice president of [redacted].[vi]

> *"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 "[redacted]" participated in voting. According to the IRB membership rosters, [redacted] was not a member of the IRB when these meetings were conducted."*

IRB RESPONSE: BioMed IRB did not allow non-members to vote. BioMed updates the roster after it has been accepted by OHRP. Member [redacted] was voted to join the IRB[vii] on April 6, 2011 and was added to the OHRP-approved roster on June 17, 2011, which was within the 90-day allowed window to report any implemented changes to the IRB to OHRP[viii]. To prevent this lag in the roster for distribution, BioMed IRB has decided to change the roster for client distribution immediately as a change has been made, with the statement "OHRP registration pending" and revised with "OHRP registered" once the update has been accepted.[ix]

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

IRB RESPONSE: As referenced in the previous response to 1.B.i., BioMed IRB did not allow non-members to vote. Member [redacted] was voted onto the IRB on June 30, 2010[x], and was listed on the OHRP registered roster September 8, 2010[xi]. This was within the 90-day allowable window to report any changes to the IRB to OHRP after it has been implemented. Please see the above response for the CAPA on this item.

FDA Violation 2: "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 received '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 5 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 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."

IRB RESPONSE: The term "routinely limited voting" was the term used in the 483, and therefore in our response we used that term as well, even though that does not, in our opinion, adequately describe the practice. From our September 1, 2011 letter,

> As our IRB promotes letting members type their own minutes, sometimes our members volunteer to be a part of the discussion but choose not to type their own meeting minutes. We want our members to have their own opinion and to avoid influencing their votes, they decide by inputting their own vote of whether to approve or disapprove the study or submission.
>
> As explained above all the members / observers who are present during the meeting are fully allowed to participate in the discussion. Their concerns are captured in the meeting minutes, even if within the summary for each item. Our minutes show that all the members present are allowed to participate in the discussion.

BioMed IRB had not routinely required all members attending to vote because our members were strictly volunteers, and some members preferred to participate in the discussion, or were attending by phone without computer access, and could not type their own minutes (which we required to count each vote). In these instances, the expertise and comments from the members attending but not voting were captured by an IRB staff member, and taken into consideration by the voting members when making a determination. Some committee members were also members of the staff (as designated reviewers) and sometimes would attend the meeting to present their review(s) only. Consistent with this practice and as noted in the table of meeting dates and attendees, [redacted] and [redacted] were members of the BioMed staff who were presenting items and not present for the entire meeting. Additionally, [redacted] was in training to become a primary reviewer at this meeting and presenting only and not a primary member at this point ([redacted] became a primary member on September 29, 2010.)

Although our September 1, 2011 letter attempted to defend and explain our actions, we have, since the FDA inspection, required that any primary member present at the meeting be required to vote. In addition to requiring any primary member attending or participating to vote, SOP 402 was modified on September 22, 2011[xii] to remove the quoted portion in the warning letter. ("*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*"). We emphasize that our revised SOP ensures that if a primary member is in the room they are required to vote.

BioMed recognizes that it is not common practice at an IRB for IRB committee members to also be members of the regulatory staff, and we have removed all staff as primary members of the IRB. Members of the IRB staff still act as alternate voting members of the IRB.

> *"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 meting. 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 [redacted], and [redacted], and alternate member [redacted]. At this meeting, primary member [redacted] 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 [redacted], and [redacted], and alternate member [redacted]. The meeting minutes show that primary member [redacted], who did not receive the materials according to the 'Memorandum,' voted at the meeting. Member [redacted], 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."

IRB RESPONSE:

As we had described in our September 1, 2011 letter, (and acknowledged by FDA in the warning letter):

> In order to prevent the confusion regarding who receives the memorandum we are moving towards an email notification only to all the members instead of a memorandum to be able to check the agenda from home using our VPN client or receive the meeting materials via other means, if requested.

In the CAPA memorandum, dated Aug 11, 2011 and handed to Janet White and Allen Hall during the inspection, as well as the amended CAPA, dated September 1, 2011 (sent with original response dated September 1, 2011[xiii]), it was indicated that distribution of the agenda by electronic means or VPN access had already been implemented. As a further improvement to that system, as of three weeks ago, we have been using and are in the process of testing the software "GoTo Training" to upload meeting materials (protocols and informed consents). We have utilized the GoTo Training software to invite members to the upcoming meeting and to provide a secure place to view the meeting materials and keep a record of who views the materials. The print out from the website showing past scheduled meetings is attached.[xiv]

FDA Violation 3: "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 issue 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 minutes." [Table not shown]

IRB RESPONSE: After the August, 2011 FDA inspection, we implemented a software change that displays the actual names instead of coded identities of the persons voting. Within the comments of each person who is part of a quorum, their vote is captured. The software change affects the minutes retroactively, if reprinted, and we have included the reprint as a corrective action included with this letter.[xv] The original way to print is retained in the database to be used only be on an item-by-item basis if the need to protect confidentiality of members arose and to print within individual files.

> *"B. Minutes are not sufficient to show actions taken by the IRB and the vote on these actions including the number of members voting or, 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 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."

IRB RESPONSE: During the time period from December 9, 2009 to April 7, 2010, the practice of creating the record of meeting minutes in paper form was to print meeting minutes form our database after the meeting and put them in a binder. Due to the way that our database captures minutes, each set of comments is linked to an "action" (each document in a submission) and the action is either open to accepting comments or closed to accepting comments. During your inspection from September 22, 2010 to October 25, 2010, it was brought to our attention that the original and follow up minutes to a conditional approval only appeared in the resolution date of the minutes. At that time, the corrective action was focused on improving the clarity of follow up conditions imposed by the IRB and documentation within of approval letters.

Currently we are striving to improve the actual printed record. While internally, we find it useful to have the progression of votes on a particular item viewed together in the database, we did not realize the limitations of technology on how it would appear when printed. Theoretically, if minutes were printed before the next meeting, the "conditionally approved" determination would have been printed with that meeting date, but as we now realize, would also appear in the "re-opening" of the item that is dated according to the date the submission was approved (conditions were satisfied). To ensure that the audit record is clearer, we have changed our process to create a new "action" instead of re-opening the item even though it is part of the same submittal. The revised Work Instruction is included as an attachment to this letter.[xvi]

"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 at total of only two votes.

In your January 12, 2012 letter, as a corrective action you propose generating an additional 'truncated yet still official set of minutes' for FDA's review. Creating multiple sets of 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."

IRB RESPONSE: The summary of votes section is mainly used as a tool for the IRB staff for quick reference while preparing documents to be distributed. There is a summary of votes and

minutes for each item linked to a document in our database and for the agenda that our staff creates. Our actual summary of who attended for the meeting as a whole is the "new agenda" item that is written by a staff member of the IRB. The full printout of minutes and the "new agenda" (included here for reference) shows who voted for each item, and within the comments section also shows their determination. The word truncating was used in the sense of raw data captured by our software, and was not intended to refer to actions required of the IRB within the code of federal regulations, (i.e. the content available for audit by the FDA). The minutes created by the software change would be the official set of minutes for audit. The reference to another way to print would only be on an item-by-item basis if the need to protect confidentiality of members arose.

> *"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."*

IRB RESPONSE: The way that BioMed IRB records minutes is that each voting member types his or her own comments directly into a database, to ensure that the vote is not influenced by other members and that the comments that each member feels are important to note, are entered into record. The staff member is there to provide a "summary" of the conversation. In the staff members minutes[xvii]

> A long converstaion addresses the ethical question of price/payment in regards to how much is ethical to ask someone to pay. FDA says that the payment cannot be more than what it costs to run the trial, and the site is not charging for this investigational portion. Further discussion about compensation and paying and ethics with this population, it has to up to the subject as far as if you would pay for another month, and if you only have one month to live. Does it matter if the person will return to be a functional member of society (return to work, etc)? We cannot make that call, we must let the study proceed to discover this fact. There must be a substantial potential benefit to the subject and we have not determined that as of yet. Preliminary data looks promising but it needs more time to really say or make a judgement.
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> 88: I am a little bit concerned about how fast they are increasing the dose
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> 77: The site has waited until the 3rd person finished.... The PI would argue as well that a non-therapeutic dose is not ethical as an additional [dose]. The other thing is that most of these subjects did not have more than a month to live.

In this case, the IRB did not feel that they could make the decision for the subjects in regards to payment "it has to be up to the subject as far as if you would pay for another month, and if you only have one month to live." When the minutes for this item are read as a whole, BioMed believes that the resolution is within the minutes and the staffers minutes for the question of increasing the dose. The site was increasing the dose as subjects were enrolled, if there were not serious events, and the protocol had been sent to the FDA. In our most recent training on staff

minutes[xviii], it was emphasized to follow up on any controversies that were in the minutes of the members.

Included with this response is the copy of our letter to clients informing them of the restrictions placed on us. We are sending the warning letter and the response as well as the notification, and the warning letter has been posted on our website since March 29, 2012.

Thank you for providing us the opportunity to clarify and address your concerns about the operations of BioMed IRB in the oversight of FDA regulated clinical investigations. We look forward to your response.

Sincerely,

Amelia Cline

BioMed IRB, by Amelia Cline as IRB Administrator

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[i] [redacted]esume 2010, page 1 "Professional experience"
[ii] [redacted] Resume 2010, page 1 "Professional experience"
[iii] July 7, 2010 minutes, "block 1", protocol [redacted]
[iv] [redacted]Resume 2010, page 3 "Other Awards/Accomplishments"
[v] [redacted] Resume 2010, page 1 "Professional experience"
[vi] [redacted]'s statement of experience
[vii] "Action View" from meeting April 6, 2011 for EE to join IRB
[viii] OHRP website "IRB Registration Process-FAQ"
[ix] Revised Work Instruction "OHRP Registration"
[x] June 30, 2010 "Action View" for special agenda item to DH to join IRB
[xi] PDF generated based on OHRP approved membership roster for client distribution
[xii] SOP 402, Version 5.0
[xiii] FDA 483 response dated September 1, 2011
[xiv] Screen Shot "GoTo Training"
[xv] Reprint of minutes for meetings dated 12/09/09, 04/07/10, 06/29/11 (note: in order to focus on the specific violation, only one day within a week of items including expedited and committee approved items and may not include all expedited determinations or any non regularly scheduled meetings)
[xvi] Revised Work Instruction "IRB Actions"
[xvi] Meeting minutes, item Study 2, October 7, 2010.
[xvi] Staff training on minutes, February 3, 2012

Cc: Alonza Cruse, District Director, HFR-PA200
Food and Drug Administration
19701 Fairchild
Irvine, CA 92612

Cc: Kristina Borror, Ph.D., Director
Divison of Compliance Oversight
Office for Human Research Protections
1101 Wooton Parkway, Suite 200
Rockville, MD 20852