



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

By Certified Mail-Return Receipt Requested  
And by Facsimile Transmission

CBER-06-008

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

Warning Letter

JUL 10 2006

Maribeth D. Snapp, Chairperson  
Oklahoma Blood Institute Institutional Review Board  
1001 North Lincoln Boulevard  
Oklahoma City, Oklahoma 73104

Dear Ms. Snapp:

This letter describes the results of a Food and Drug Administration (FDA) inspection of the Oklahoma Blood Institute (OBI) Institutional Review Board (IRB) that was conducted from February 14 through 27, 2006. FDA investigator Margaret Annes visited the IRB to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 56. The inspection was 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 FDA investigator issued and discussed the Form FDA 483, Inspectional Observations, with you and other staff members of OBI at the end of the inspection. We reviewed the inspection report, the Form FDA 483, and your letter dated March 15, 2006 in response to the Form FDA 483.

We have determined that the IRB significantly violated applicable federal regulations governing the operation and responsibilities of IRBs as published under 21 CFR Part 56 (available at <http://www.gpoaccess.gov/cfr/index.html>). The applicable provisions of the CFR are cited for each violation. We are addressing this letter to you under 21 CFR 56.120(a) as the current IRB Chairperson with responsibility for ensuring that the IRB takes the actions necessary to bring the IRB into full compliance with FDA regulations. Under 21 CFR 56.120(a) we are also sending copies of this letter to the responsible head of the IRB's parent institution, OBI, because under 21 CFR 56.120(c), the parent institution is presumed to be responsible for the IRB's operations.

- 1. The IRB failed to review proposed research at convened meetings at which a majority of the members of the IRB were present. [ 21 CFR § 56.108(c) ].**

The initial review and approval of Protocol [REDACTED] was not conducted at a convened meeting of the IRB. The IRB approved the study by written ballot after a study sub-investigator distributed the study protocol, information sheet, consent forms, and a ballot ("Approval Form") to the IRB members. In your

March 15, 2006 response, you confirm that the IRB members returned individual approval letters for the initial version of the [REDACTED] protocol, consent form and the information sheet.

Similarly, the review and approval of an addendum to protocol [REDACTED] and the related consent form were not discussed during a convened meeting of the IRB. The minutes for the IRB meeting on 5/18/04 and the follow-up memorandum dated 5/26/04 indicate that the study materials were not distributed and discussed during the convened meeting. Instead, three IRB members signed and submitted written ballots approving the protocol addendum.

In your March 15 response, you state that the IRB Chairperson approved an addendum to the study dated May 26, 2004 by an expedited review procedure. We remind you that FDA regulations provide for the use of expedited review procedures for certain categories of research involving no more than minimal risk (see 63 Fed. Reg. 60353 (Nov. 9, 1998)), and for minor changes in previously approved research during the period for which approval is authorized. Expedited review procedures must meet the requirements set forth in 21 CFR § 56.110.

Your response also explains that the IRB plans to add additional members and increase the number of IRB meetings per year as needed to ensure that convened meetings occur before implementation of new protocols. Please provide a copy of any IRB procedures that were revised in response to the violations noted above.

**2. The IRB failed to notify an investigator in writing of its approval of proposed research. [ 21 CFR § 56.109(e) ].**

The IRB did not notify the investigator in writing that the IRB approved the study protocol, the associated consent forms, and the information sheets for the study identified in item 1, above. We also note that the IRB failed to notify the investigator of the IRB's approval of several revisions to the informed consent forms.

In your letter, you propose corrective actions, including adding more details to correspondence and recruitment of additional support personnel. Please provide a copy of any IRB procedures that were revised in response to the violation noted above.

**3. The IRB failed to prepare and maintain adequate documentation of IRB activities. [ 21 CFR § 56.115(a)(1), (a)(2), (a)(3), and (a)(4) ].**

- A. IRB meeting minutes have not been maintained in sufficient detail to show actions taken by the IRB and the vote on these actions. Examples include the minutes for the IRB meetings conducted on 10/15/02, 11/10/03, 5/18/04, 10/18/04, 3/14/05, and 5/23/05, which lack information such as

the vote on actions taken, including the number of members voting for, against, or abstaining.

- B. The IRB meeting minutes do not identify the version of the study protocols and the consent forms that the IRB discussed during the meetings. For example, the minutes for 11/10/03, 5/18/04, and 01/18/04 for a [REDACTED] study do not specify the protocol number, and at the time of the inspection the IRB was responsible for the review of three [REDACTED] studies. Without a means of clearly identifying which study is being discussed, the IRB may not be able to track the actions required by the IRB and assess the subjects' safety in the studies.
- C. The IRB failed to maintain documentation of IRB activities on research proposals such as the review of informed consent documents submitted by the investigator. For example, the IRB files did not have several versions of the consent forms for protocols [REDACTED] and [REDACTED] which were retrieved from the clinical investigator and had been marked with the IRB's approval stamp. The IRB retrieved some consent form versions from the OBI document control system and obtained some from the clinical investigator's files.
- D. The IRB failed to maintain all correspondence between the IRB and the investigators. The IRB failed to maintain an unanticipated adverse device effect submitted by the sponsor via the investigator for Protocol [REDACTED]. The IRB did not maintain documentation of the report submitted by the clinical investigator, and [REDACTED] provided a copy of the adverse device effect to the FDA investigator from the clinical investigator files.

In your letter you state that the IRB will dedicate additional personnel to maintain all IRB documentation and that you will further develop the document control system for use with research documents and IRB operations. In your response to this letter please explain how the IRB will maintain control of the IRB documentation required by 21 CFR 56.115(a) using a centralized document control system.

**4. The IRB failed to maintain and follow adequate written procedures for conducting its initial and continuing review of research. [21 CFR § 56.108(a) and 21 CFR § 56.115(a) ].**

- A. The IRB's policies and procedures dated 10/29/03 require the submission of progress reports about the research at least on an annual basis and a summary of the general course of the research. The IRB policies further require the IRB to maintain all correspondence between the IRB and the investigator. There was no documentation of any such progress reports in the IRB's files, nor was there any documentation of follow-up by the IRB regarding the failure to submit progress reports.

- B. The IRB failed to review and approve the following consent forms for the following collection sites that participated in the study [REDACTED]

Collection site	Consent form date
[REDACTED]	8/14/03
	8/20/03
	3/27/03
	3/27/03
	3/27/03
	3/27/03
	3/27/03
	3/27/03
	3/27/03

We recommend that you revise the IRB's written procedures to include (1) the duration of the IRB approval of research in IRB approval letters to the investigators for approval of research and associated consent forms, as promised in your response; and (2) a tracking number for each study that the IRB intends to review to facilitate review and recordkeeping requirements.

At the time of the inspection, the IRB filed study information by meeting date. We recommend that the IRB develop and maintain separate files for each project to facilitate the IRB's recordkeeping and review activities.

We also recommend that you consider potential conflicts of interest, and how conflicts of interest are addressed, as you increase the size of your IRB and revise your IRB procedures. We note that either Dr. Gilcher – the President, Chief Executive Officer, and Medical Director of OBI – [REDACTED] is a clinical investigator for all studies being conducted at OBI. IRB meeting minutes document that Drs. Gilcher and [REDACTED] attend all IRB meetings, participate in research discussions, and are present for voting on proposed research. [REDACTED] is also responsible for setting the meeting agenda, sending information packets and research proposals to the IRB members, sending and receiving information from the IRB members, and maintaining the IRB files. Pursuant to 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 conflicting interest, except to provide information requested by the IRB.

This letter is not intended to contain an all-inclusive list of deficiencies in the operations of the IRB.

Please notify this office in writing, within fifteen (15) business days of receipt of this letter, of the actions you have taken or plan to take to bring the IRB into compliance with FDA requirements. Please provide the requested information, and include a copy of any revised documents, such as written procedures and a revised roster with your response. Also, for any plans of action, please include the projected completion dates for actions to be accomplished.

Your failure to adequately respond to this letter may result in further administrative actions against your IRB, as authorized by 21 CFR 56.120 and 56.121. These actions could include FDA withholding approval of new studies reviewed by your IRB that are subject to Parts 50 and 56 of the FDA regulations, prohibiting the admission of new subjects to ongoing studies that are subject to 21 CFR Parts 50 and 56, terminating all ongoing studies approved by your IRB, and initiating regulatory proceedings for disqualification of your IRB.

Please send your written response to:

Ms. Bhanu Kannan  
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) 827-6221

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

Sincerely,



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

Cc: Michael Chappell, District Director  
Food and Drug Administration  
4040 N. Central Expressway, Suite 300  
Dallas, Texas 75204

Ronald O. Gilcher, M.D.  
President, CEO, and Medical Director  
Oklahoma Blood Institute  
1001 N. Lincoln Blvd.  
Oklahoma City, Oklahoma 73104

Kristina Borrer, Ph.D., Director  
Division of Compliance Oversight  
Office for Human Research Protections  
1101 Wootton Parkway, Suite 200  
Rockville, MD 20852