Inspections, Compliance, Enforcement, and Criminal Investigations

Texas Applied Biomedical Services 9/24/12

Department of Health and Human Services

Public Health Service
Food and Drug Administration
Center for Biologics
Evaluation and Research
1401 Rockville Pike
Rockville, MD 20852-1448

September 24, 2012

By Facsimile Transmission and Overnight Delivery CBER- 12- 09

Ms. Mildred Joyce Heinrich, President/Chairperson
Texas Applied Biomedical Services
dba Texas Applied Biotechnology Research Review Committee IRB
dba TABS Research Review Committee IRB # 1
12101 Cullen Boulevard, Suite A
Houston, Texas 77048

Warning Letter

Dear Ms. Heinrich:

This letter describes the results of a Food and Drug Administration (FDA) inspection of the Texas Applied Biomedical Services Research Review Committee (TABS RRC) that concluded on April 25, 2012. The FDA investigator conducted the inspection of this Institutional Review Board (IRB) to determine if the IRB's activities and 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 FDA conducted this inspection under its Bioresearch Monitoring Program, which includes inspections designed to review IRB operations relating to clinical studies of FDA regulated products and to ensure that human subjects are protected from undue hazard or risk during the course of clinical studies.

At the end of the inspection a Form FDA 483, Inspectional Observations, was issued and discussed with you. We reviewed the inspection report, the Form FDA 483 and your letter dated May 11, 2012, sent 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). This letter requests prompt corrective action to address the violations cited and discusses your IRB's written response to the noted violations.
The applicable provisions of the CFR are cited for each violation.

1. The IRB failed to ensure that no member participated in the initial or continuing review of a project in which the member had a conflicting interest. [21 CFR § 56.107(e)].

The TABS RRC procedures manual, *RRC Membership,* states that no member of the Committee shall be involved in either the initial or continuing review of an activity in which he or she has a conflicting interest, except to provide information requested by the reviewing body. The meeting minutes dated January 26, 2012, show that two of the **(b)(4)** committee members, including you as the Chairperson, participated in the initial review and approval of clinical studies sponsored by **(b)(4)** (hereafter, **(b)(4)**) in which the members had a conflict of interest. Both you and **(b)(6)** voted to approve protocols sponsored by **(b)(4)** even though you had both provided consulting services to **(b)(4)**, assisting with writing protocols and informed consent documents, for which payment was requested.

In your letter, you disagree with the observation that TABS IRB members had a conflict of interest with the review of the **(b)(4)** clinical studies. You explain that one of the IRB committee members assisted in the initial drafting of the **(b)(4)** clinical study protocols and that consulting services provided to **(b)(4)** by Texas Applied Biomedical Services and/or J Heinrich Consulting are not conflicts of interest. You further explain that the consulting services provided to **(b)(4)** "were maintained separate and apart from any TABS Research Review Committee functions and actions."

We disagree with your explanations. The two members in question had a conflicting interest when they participated in the initial review and approval of the protocols and informed consent documents which they assisted in drafting. Conflicting loyalties, whether conscious or not, may influence the IRB's deliberations.

2. The IRB failed to prepare, maintain and follow its written procedures for conducting its initial and continuing review of research. [21 CFR §§ 56.108(a) and 56.115(a)(6)].

The IRB does not have a written procedure regarding the IRB's method of reviewing protocols and consent forms to ensure safeguards are in place for children who participate in a clinical study. The meeting minutes dated January 8, 2012, show that the IRB approved an investigational **(b)(4)** study involving children **(b)(4)** years old.

In your letter, you acknowledge that TABS RRC had not previously reviewed clinical investigational research studies involving pediatric subjects. You also state that an SOP (standard operating procedure) will be written addressing pediatric clinical studies in accordance with 21 CFR Parts 50 and 56. In your response to this letter please submit a copy of your new SOP addressing clinical studies involving pediatric populations.

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

The IRB did not possess the professional competence necessary to provide complete and adequate review of the specific research activities. For example:

> A. On January 8, 2012, the IRB reviewed and approved an investigational **(b)(4)** study involving pediatric and adult subjects with disorders of the **(b)(4)**. 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." The IRB did not include an individual with professional competence in the treatment of **(b)(4)** disorders (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)
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> B. On January 26, 2012, the IRB reviewed and approved two studies involving subjects with **(b)(4)** The IRB did not include an individual with professional competence (e.g. a physician) i

the treatment of **(b)(4)**, nor is there any documentation to indicate 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).

In your letter, you disagree with this observation. You explain that TABS IRB does not have a medical doctor as an active, regular voting member of the committee, but the committee has access to a core group of medical advisors that provide expertise and input for any and all clinical research studies the committee encounters. Your letter also states an independent consultant with extensive experience in **(b)(4)** research was consulted when the IRB reviewed and approved two studies involving subjects with **(b)(4)**

We note that the meeting minutes dated January 26, 2012, failed to include documentation of any consult with a **(b)(4)** specialist that was taken into account by the IRB committee in its decision to approve the studies. In your response to this letter please provide documentation of the independent consultation to the IRB.

4. The IRB failed to determine that a pediatric study is in compliance with Part 50 Subpart D. [21 CFR §§ 56.109(h) and 56.111(c)].

Under 21 CFR Part 50 Subpart D, Additional Safeguards for Children in Clinical Investigations, IRBs are required to review clinical investigations involving children as subjects covered by Subpart D and approve only those clinical investigations that satisfy the criteria within certain risk categories identified in sections 50.51, 50.52, or 50.53 under Subpart D.

A. The meeting minutes from January 8, 2012, show that the IRB reviewed and approved an investigational **(b)(4)** study involving children. The meeting minutes do not document the IRB's determination of the level of risk involved, the potential for direct benefit, the likelihood of yielding generalizable knowledge about the subjects' disorder or condition, and the opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

B. The meeting minutes from January 8, 2012, do not document that the IRB discussed and/or determined adequate provisions were made for soliciting the assent of the children involved in the investigational **(b)(4)** study.

In your letter you state that all future studies involving pediatric subjects will be more closely scrutinized. Also in your letter you reference an FDA Guidance for IRBs and Clinical Investigators - Informed Consent Document Content which provides that FDA does not require the informed consent document to contain a space for assent by children. We do not accept your explanation. The observation on the Form FDA 483 does not speak to whether FDA requires the Informed Consent document to contain a space for assent by children. Instead, the FDA investigator observed that the IRB failed to determine at the time of the initial review that the research study was in compliance with 21 CFR Part 50 Subpart D. Additionally, please note that 21 CFR Part 50, Subpart D requires IRBs to find and then document that the clinical investigations involving children as subjects meets the requirements of Subpart D. The meeting minutes for January 8, 2012, fail to document additional requirements for review of this study involving pediatric subjects.

5. The IRB failed to prepare and maintain adequate documentation of IRB activities. [21 CFR § 56.115].

A. The IRB did not maintain meeting minutes for 2011. During the inspection you told the FDA investigator the IRB met twice in 2011. According to your study list, protocol TABS **(b)(4)** was modified and approved on August 24, 2011, but no meeting minutes were available for review documenting the IRB's activities.

In your letter, you confirm that there are no meeting minutes for 2011 during which two meetings

were held. You explain that due to a computer crash all minutes and data for that time frame were lost. You stated that you would "re-create" the meeting minutes and provide them at a later date.

It is inappropriate and an unacceptable record keeping practice for the IRB to re-create minutes for 2011. In your response to this letter, please provide proposed corrective actions to prevent future occurrence of the loss of required records.

> B. The IRB failed to maintain meeting minutes with sufficient detail to show actions taken by the IRB and the vote on these actions. The meeting minutes from January 8, 2012, fail to show which of the **(b)(4)** IRB members present at the meeting voted for, against or abstained. The IRB reviewed and approved an investigational **(b)(4)** study during the January 8, 2012, meeting however the meeting minutes do not document that the IRB reviewed and agreed with the sponsor's determination of the risk status of the investigational **(b)(4)** to be used in that study.

In your letter, you stated there was an oversight in transcription for the January 8, 2012, meeting minutes in recording each member's vote. Your letter also states that you will ensure more complete minutes in future meetings by assigning a clerical person to act as recording secretary for the IRB meeting.

The IRB's failure to maintain meeting minutes in accordance with 21 CFR 56.115(a)(2) is a repeat violation identified in the last two FDA inspections conducted in 2007 and 2000. Given the past failure to correct this deficiency, in your response to this letter please explain what steps the IRB has taken to ensure meeting minutes will be maintained in accordance with the regulations. In addition please submit a copy of the IRB's meeting minutes for all meetings conducted since April 25, 2012.

> C. The IRB failed to maintain IRB membership rosters for 2008 through 2012 in accordance with 21 CFR 56.115(a)(5). The IRB membership rosters do not identify members by their representative capacity and any employment or other relationship between each member and the institution. This is a repeat violation identified during the FDA inspection conducted in 2000.

In your letter, you submitted a revised membership roster dated May 11, 2012. The revised roster fails to comply with the regulations because it does not indicate that you are an affiliated member even though you are the president of TABS, Inc. and Chairperson of TABS RRC. In addition, **(b)(6)** is listed as a non affiliated member, but immediate family members of an employee of the institution cannot be deemed to be nonaffiliated under 56.107(d).

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 repeated deficiencies found during the last three inspections, 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**
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> · **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 as FDA has evidence of adequate corrective actions and notifies you in writing that the IRB's corrective actions are satisfactory. 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 actions you have taken or plan to take to bring the IRB into compliance with FDA requirements. 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. If you do not believe your IRB is in violation of FDA requirements, include your reasoning and any supporting information for our consideration.

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. Please also provide an updated list of all studies being reviewed by your IRB, identify those that are subject to 21 CFR Part 56, and list all studies that are affected by the above restrictions.

Your failure to respond to this letter, or implement adequate corrective action, may result in FDA taking further administrative actions, as authorized by 21 CFR 56.120, 56.121, and 56.124. 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:

Lillian Ortega
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, MD 20852-1448
Telephone: (301) 827-6335

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

Sincerely,
/S/

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

Page Last Updated: 10/15/2012
Note: If you need help accessing information in different file formats, see Instructions for Downloading Viewers and Players.

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