

**By Hand Delivery****SEP 16 2014**

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

Notice of Opportunity for Hearing

Dear Ms. Heinrich:

The Center for Biologics Evaluation and Research (CBER or the Center), Food and Drug Administration (FDA) has information indicating that TABS Research Review Committee IRB (TABS RRC or the IRB)¹ has refused or repeatedly failed to comply with the regulations set forth in Title 21 Code of Federal Regulations (CFR), Part 56, and the noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation. The violations and the effect of the noncompliance on human subjects provide the basis for disqualification of TABS RRC.

Pursuant to 21 CFR § 56.120, the Center informed you, by letter ("Warning Letter") dated September 24, 2012 of the specific matters complained of and offered you an opportunity to respond to them in writing. That letter placed the following restrictions on the activities of TABS RRC, in accordance with 21 CFR §§ 56.120(b) (1) and (2), effective upon issuance of the letter:

- **FDA is withholding 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.**

Prior to responding to the Warning Letter, you called the designated CBER representative on September 27, 2012 to discuss the Warning Letter and your proposed written response. The CBER representative returned your call on September 27, 2012 and answered your questions pertaining to certain confidentiality issues, as well as questions relating to meeting minutes from 2011 that were lost. You responded to the Warning Letter in letters dated October 8, 2012 and October 19, 2012.

¹ TABS Research Review Committee is the name under which this IRB is registered with the Office of Human Research Protections, Department of Health and Human Services:
<http://ohrp.cit.nih.gov/search/search.aspx?styp=bsc>. This IRB has conducted business as Texas Applied Biomedical Services, Texas Applied Biotechnology Research Review Committee IRB, and TABS Research Review Committee IRB #1

On November 8, 2012, CBER became aware that while the IRB was under FDA's restrictions, TABS RRC had reviewed and determined the (b)(4) to be a (b)(4). On November 13, 2012, the CBER representative called and emailed you requesting all documents reviewed and the meeting minutes supporting the IRB's November 7, 2012 (b)(4) for the (b)(4). You responded in a letter dated November 14, 2012.

After reviewing your three letters, FDA continued to have serious concerns about whether the TABS RRC's proposed corrective action plans were adequate to bring the operations of the IRB into compliance with FDA regulations at 21 CFR Part 56. As a result, FDA requested a regulatory meeting to discuss these issues with you. On February 22, 2013, FDA representatives and TABS RRC held a regulatory meeting via videoconference to discuss and request additional clarification regarding TABS RRC's corrective action plans to attain compliance, including the IRB's structured approach to maintain long-term compliance with federal regulations. During the February 22, 2013 regulatory meeting, FDA expressed concern about your proposed corrective actions included in your written letters and described verbally during the meeting, including the following:

- The implementation of the new TABS RRC SOP No. 104 *Application of Conflict of Interest*.
- Your conflict of interest as an active participant in both (b)(4) (a clinical research consultation service) and TABS RRC (an Institutional Review Board).
- TABS RRC's failure to bring the IRB's membership into compliance with FDA regulations.

At the conclusion of the regulatory meeting, FDA requested the following: (1) documentation supporting TABS RRC's updated proposed corrective actions; (2) revised Standard Operating Procedures; (3) updated membership and medical advisory core rosters; (4) training records; (5) copies of all signed Conflict of Interest Statements; and (6) a listing of all IRB activities since September 24, 2012, the date of the Warning Letter. You responded in letters dated March 18, 2013 and May 30, 2013.

The Center has reviewed your letters and finds acceptable your corrective actions for the following matters:

1. Item 2 on page 2 of the Warning Letter, regarding the IRB's method of reviewing protocols and consent forms for pediatric subjects.
2. Item 4 on page 3 of the Warning Letter, regarding the IRB's failure to determine that a pediatric study was in compliance with Part 50 Subpart D.
3. Item 5C on page 5 of the Warning Letter, regarding the IRB's membership roster identifying each member's affiliation.

The Center has concluded that your written and verbal explanations for the remaining matters cited in the Warning Letter are unacceptable because they fail to adequately correct the violations. In other words, TABS RRC has failed to take adequate steps to correct the noncompliance stated in the Warning Letter dated September 24, 2012 issued under 21 CFR 56.120 (a).

On December 23, 2013, FDA sent you a follow up letter identifying the following: (1) items cited in the Warning Letter to which you failed to provide adequate corrective actions; (2) your repeated failure to bring the operations of the IRB into compliance after receipt of the September 24, 2012 Warning Letter. Furthermore, the follow up letter reminded you that whenever an IRB has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under 56.120(a), the Commissioner of Food and Drugs may determine that this noncompliance justifies the disqualification of the IRB. You

replied via email on December 23, 2013 with the following: “I will follow up on my response to the continued concerns listed in your letter dated December 23, 2013.” To date FDA has not received a response from TABS RRC.

Because of your continued failure to take appropriate corrective action, this noncompliance justifies disqualification. Accordingly, FDA is instituting proceedings to disqualify TABS RRC and TABS RRC is being offered an opportunity for a regulatory hearing under 21 CFR Parts 16 and 56, regarding the question of whether TABS RRC should be disqualified. TABS RRC has the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in 21 CFR Part 16 and FDA’s regulations on electronic media coverage of administrative proceedings, 21 CFR Part 10, Subpart C. Enclosed you will find copies of these regulations.

A listing of the specific violations follows. These are the matters that would be considered at a regulatory hearing, if a hearing is requested and granted. Applicable provisions of the CFR are cited for each violation.

1. The IRB failed to adhere to the restrictions imposed under 21 CFR § 56.120 (b) (2).

- A. In the September 24, 2012 Warning Letter, FDA informed you that no new subjects are to be enrolled in any ongoing studies subject to 21 CFR Part 56 and approved by the IRB, effective upon issuance of the letter. TABS RRC approved the following clinical investigational study protocol sponsored by (b)(4) entitled (b)(4) (b)(4) (b)(4) on December 15, 2010. This study, which had been approved by the IRB, was ongoing upon your receipt of the September 24, 2012 Warning Letter. Despite this restriction, you failed to inform the sponsor of the imposed restrictions on your IRB activities. The sponsor continued to enroll new study subjects in the study. Thirteen new study subjects were enrolled in the (b)(4) study after September 24, 2012.

In the September 24, 2012 Warning Letter, FDA requested that you send a copy of your written communication to each of the affected sponsors and clinical investigators notifying them of your current FDA imposed restrictions. In addition, FDA requested an updated list of all studies being reviewed by your IRB, identifying those that are subject to 21 CFR Part 56, and list all studies that are affected by the above restrictions. Your October 8, 2012 letter does not list (b)(4) (b)(4) as a sponsor to whom the FDA imposed restrictions were sent nor did you list the above study in the Clinical Studies currently under review by TABS RRC listing.

Your failure to adhere to FDA’s imposed restrictions demonstrates your unwillingness or inability to comply with FDA regulations [21 CFR 56.120(b)]. Your failure to notify (b)(4) (b)(4) of your Warning Letter and imposed restrictions adversely affects the rights and welfare of the human subjects in the above clinical investigation reviewed by your IRB.

2. 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)].

- A. 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 indicate 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)(4) 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.

- B. Meeting minutes dated November 7, 2012 show that you, as the IRB Chair, voted for the (b)(4) of the (b)(4) submitted by (b)(4) despite the fact that you, as the (b)(4) a clinical research consultation service, filed four submissions with FDA on behalf of (b)(4) These were (b)(4) In your role as the Chairperson, you conducted a “special” meeting on November 7, 2012 by email and telephone calls to individual members, to vote on a (b)(4) for the (b)(4) (b)(4). Individual members gave you feedback by telephone or in emails. Emails and/or individual telephone conversations do not constitute a convened meeting as they do not support active participation and discussion between IRB members. Your decision to conduct the “special” meeting via email and telephone rather than to hold a convened meeting in accordance with FDA regulations (21 CFR 56.108(c)) - even after receipt of the Warning Letter demonstrates your inability or unwillingness to take adequate steps to bring your IRB into compliance.

(b)(4) role as a consultant for (b)(4), Inc. is in direct conflict of interest with her role as an IRB voting member when the IRB reviews proposed research of the sponsors, and individuals for whom she also provides consulting services. In addition, your role as the (b)(4) is in direct conflict of interest with your role as the Chairperson of TABS RRC when the IRB reviews proposed research of the products, sponsors, and individuals for whom you also provide consulting services.

The IRB’s proposed corrective actions for this observation includes the implementation of new TABS RRC Standard Operating Procedure No. 104 *Application of Conflict of Interest* and a plan to have each committee member and alternate sign a Conflict of Interest Statement when they initially become a board member, and annually thereafter.

Your proposed corrective actions will not prevent the recurrence of this or similar violations in the future. The IRB’s proposed corrective actions are inadequate for the following reasons: (1) The IRB has failed to recognize and resolve the conflict between your involvement as (b)(4) (b)(4) and your responsibilities as Chairperson for TABS RRC; (2) TABS RRC Procedure manual *Application of Conflict of Interest* states “In situations where the committee member detects the possibility of a conflict of interest, the committee member should declare this possibility to the IRB Chairperson and (in a discussion with the IRB) make a decision about whether or not to excuse him/herself.” The procedure manual does not clearly state that when it is determined that there is a conflict, whether the IRB Chair alone makes the decision that an IRB member is conflicted or whether it is in conjunction with all other IRB board members. The procedure manual does not explain the steps the IRB will take to ensure that when an IRB member is deemed to have a conflict, they do not participate in the initial or continuing

IRB review for the project. Additionally, the procedure manual fails to address how the IRB will review a potential conflict of interest of the IRB Chairperson.

In order for an IRB to assure that appropriate steps are taken to protect the rights and welfare of human subjects participating in research, the IRB must ensure that members with conflicting interest do not participate in the initial and continuing review of such research. TABS RRC repeatedly allowed its board members to participate in the initial and continuing review of projects in which they had a conflicting interest. The IRB's repeated failure to comply with FDA regulations [21 CFR 56.107(e)] adversely affects the rights and welfare of the human subjects in clinical investigation reviewed by the IRB.

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

The IRB does not possess the professional competence necessary to provide complete and adequate review of the research activities commonly reviewed by this IRB. For example:

- A. On January 8, 2012, the IRB reviewed and approved an investigational (b)(4) study involving both pediatric and adult subjects with disorders of the (b)(4) (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) (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 the study, as permitted by 21 CFR 56.107(f).
- 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) in the treatment of (b)(4) (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).
- C. On July 26, 2012, the IRB reviewed and approved an investigational (b)(4) study involving subjects with (b)(4). Review of the IRB records indicates that the IRB lacked the professional competence necessary to review this study. The IRB did not include an individual with professional competence (e.g., a physician specializing in (b)(4)) in the treatment of (b)(4).

Because an IRB must be sufficiently qualified through experience and expertise to review specific research activities, an IRB must retain the necessary expertise to effectively review each protocol it receives. According to the IRB records, TABS RRC reviews clinical investigations involving medical devices for adult and pediatric use, as well as biological products for adult use. However, IRB records indicate that the IRB lacked the professional competence necessary to review these studies and determine whether they 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."

Your letter dated October 8, 2012 explains that TABS RRC 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 provides expertise and input for any and all clinical research studies the committee encounters. During the regulatory meeting held on February 22, 2013 and in your letter dated March 18, 2013, you stated that TABS RRC is exploring the addition of licensed medical professionals as active members and the interview process for this activity is underway. To date, the updated IRB membership rosters do not indicate that a licensed medical professional has been added as an active IRB voting member; however, TABS RRC has advised us that the IRB has added two medical doctors to the IRB's consultant/medical advisor group.

Ad hoc consultants are not IRB members -- they assist in the review process but because they are not IRB members, they are not permitted to vote. They do not contribute sustained experience and medical expertise to the IRB membership. The decision of an IRB must represent the judgment of the members of the IRB. TABS RRC's repeated failure to retain the professional competence necessary among active voting members adversely affects the rights and welfare of the human subjects in clinical investigation reviewed by the IRB.

As a result, the IRB's corrective actions are inadequate because you have not resolved the lack of professional competence among the active voting IRB members necessary to completely and adequately review research activities.

4. 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 that 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 to document the IRB's activities during that year.

You explained to the FDA investigator that, due to a computer crash, all minutes and data for 2011 were lost. During the September 27, 2012 telephone conversation with an FDA representative, you offered to recreate the meeting minutes from the IRB's handwritten notes of the 2011 meeting minutes. FDA requested that you submit the handwritten notes themselves rather than to create a typed version of the lost minutes. Nonetheless, you submitted a typed version of the 2011 handwritten notes with your letter dated October 19, 2012. As we stated in the Warning Letter, it is inappropriate and an unacceptable practice to recreate meeting minutes.

In your October 8, 2012 letter, you described the "implementation of the new electronic back-up system to capture all data files and documentation thereby to ensure availability of all information relative to the clinical research projects in the future." The IRB's response is inadequate because you did not provide documentation (e.g., SOPs, etc.) explaining how minutes and study files will be stored and/or protected to prevent the loss of required documentation in the future.

The IRB's failure to maintain meeting minutes in accordance with 21 CFR 56.115(a) (2) is a repeat violation. It had also been identified in the last two FDA inspections conducted in 2000 and 2007.

- B. In your October 8, 2012 letter you explain that, effective September 15, 2012, the IRB implemented a new template identifying the information to be recorded to ensure that the minutes of future IRB meetings are in compliance with 21 CFR 56.115(a)(2). TABS RRC Procedure manual *RRC Meeting Forms* states “Minutes of IRB meetings should include sufficient detail to show: Item 2.b. Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions. Item 3. Presence of a quorum throughout the meeting. Item 4 h. Determinations of conflict of interest, if any.”

On November 7, 2012, TABS RRC failed to follow the newly implemented template submitted to the FDA as a corrective action. The November 7, 2012 meeting minutes did not document (1) the confirmed receipt of pertinent materials by all IRB members prior to the meeting, nor (2) the presence of quorum throughout the meeting. In addition, (b)(4) (b)(4) was listed as an IRB member who abstained since he requested the review, but (b)(4) conflict of interest was not documented in the meeting minutes.

- C. At the conclusion of the regulatory meeting on February 22, 2013, FDA requested all documentation of IRB activities conducted by TABS RRC since FDA’s restrictions were imposed on September 24, 2012. During the meeting you explained that TABS RRC received a (b)(4) study in December 2012, and that you referred the protocol to another IRB. FDA requested that you submit the research protocol reviewed by TABS RRC and all documentation of IRB activities and decisions regarding this research proposal. The IRB failed to respond to the FDA request for this information, except for stating that the committee did not meet in October or December 2012.

The IRB is responsible for preparing and maintaining adequate documentation of IRB activities. Such documentation provides significant evidence of whether procedures utilized by the IRB are adequately protecting the human subjects of the investigations it is reviewing. The IRB’s repeated failure to prepare and maintain documentation of IRB activities adversely affects the rights and welfare of the human subjects in clinical investigation reviewed by the IRB.

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

- A. The TABS RRC Procedure manual *RRC Meeting Forms*, effective September 15, 2012, states “the Committee will meet at a time and place as deemed by the Committee Chairperson in accordance with the Research Review Committee procedure defined in this Procedure manual.” In your role as the Chairperson, you conducted a “special” meeting on November 7, 2012 by email and telephone calls to individual members to vote on a (b)(4) for the (b)(4). The IRB committee did not have a convened meeting at a specific time or place to review and approve the (b)(4) for the (b)(4). (b)(4) Individual members gave you feedback by telephone or in emails. Emails and/or individual telephone conversations do not constitute a convened meeting.
- B. In your October 8, 2012 letter you explain that, effective September 15, 2012, the IRB implemented a new template identifying the information to be recorded to ensure that the

minutes of future IRB meetings are in compliance with 21 CFR 56.115(a)(2). TABS RRC Procedure manual *RRC Meeting Forms* states “Minutes of IRB meetings should include sufficient detail to show: Item 2.b. Names of members or alternate members who are participating through videoconference or teleconference and documentation that those attending through videoconferencing or teleconferencing received all pertinent material prior to the meeting and were able to actively and equally participate in all discussions. Item 3. Presence of a quorum throughout the meeting. Item 4 h. Determinations of conflict of interest, if any.”

On November 7, 2012, TABS RRC failed to follow the newly implemented template submitted to the FDA as a corrective action. The meeting minutes failed to document (1) the confirmed receipt of pertinent materials by all IRB members prior to the meeting; and (2) the presence of quorum throughout the meeting. In addition (b)(4) was listed as an IRB member who abstained since he requested the review, but (b)(4) conflict of interest was not documented in the meeting minutes.

- C. In your October 8, 2012 letter you provided the revised TABS RRC Procedure manual *RRC Meeting Forms* that states, effective September 15, 2012, you, the IRB Chairperson, would vote only in case of a tie.

On November 7, 2012, you held a “special” meeting by email and telephone calls to individual IRB members to vote on a nonsignificant risk device determination for the (b)(4). The meeting minutes show that you, the IRB Chairperson, voted for the (b)(4) of the (b)(4) (b)(4) however, the vote was not cast in case of a tie. You failed to follow the revised TABS RRC Procedure manual *RRC Meeting Forms* submitted to the FDA as a corrective action.

IRB written procedures are required to be established, maintained and followed to ensure the rights, safety, and welfare of human subjects. These procedures also assure FDA that the IRB has adopted human subject protection standards. Your IRB activities on November 7, 2012 demonstrate the IRB’s inability or unwillingness to adhere to the IRB’s written procedures put in place, after receipt of the Warning Letter, to bring the IRB into compliance. The repeated failure to follow written procedures violates the regulations and adversely affects the rights and welfare of the human subjects in clinical investigations.

If you choose to request a hearing, your request must be made, in writing, within ten (10) business days of receipt of this letter and is to be directed to CAPT Sharon J. McCoy, Acting Director, Division of Enforcement, Office of Enforcement and Import Operations, Office of Regulatory Affairs, Telephone 301-796-8206, Fax 301-847-8635. If no response to this letter is received by that time, TABS RRC will be deemed to have waived any right to a regulatory hearing and no hearing will be held. A decision in this matter will be made based on the facts available to FDA.

If you wish to respond but do not desire a hearing, you should submit a written response to CAPT McCoy within the specified time period stating that you waive your right to a hearing and that you want a decision on the matter to be based on your written response and other information available to FDA.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR §

16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or the Commissioner's delegate determines that no genuine and substantial issue of fact had been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

At this time, FDA has not made a final decision about TABS RRC's disqualification. Moreover, there will be no prejudgment of this matter should you decide to request a regulatory hearing or to request that the decision be based on a written submission and other information available to FDA.

Sincerely,

A handwritten signature in black ink, appearing to read "Melinda K. Plaisier", with a long horizontal flourish extending to the right.

Melinda K. Plaisier
Associate Commissioner for Regulatory Affairs

Enclosures (2)
21 CFR Part 16
21 CFR Part 10, Subpart C