

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
PROPOSAL TO DISQUALIFY
TEXAS APPLIED BIOMEDICAL SERVICES
DBA TEXAS APPLIED BIOTECHNOLOGY RESEARCH REVIEW COMMITTEE IRB
DBA TABS RESEARCH REVIEW COMMITTEE IRB #1

COMMISSIONER'S DECISION

In this proceeding, the Food and Drug Administration (FDA or the Agency), Center for Biologics Evaluation and Research (CBER), pursuant to 21 CFR 16.24 and 21 CFR 56.121, proposes to disqualify Texas Applied Biomedical Services, dba Texas Applied Biotechnology Research Review Committee IRB, dba TABS Research Review Committee IRB #1 (TABS RRC or the IRB). As the Acting Chief Scientist, I have the authority to perform all delegable functions of the Commissioner of Food and Drugs (Commissioner). For the reasons set forth below, I have concluded that TABS RRC repeatedly failed to comply with the regulations set forth in part 56 and that noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation. Therefore, I am disqualifying TABS RRC under 21 CFR 56.121(b).

I. Background

As alleged by CBER, TABS RRC had been inspected in 2000 and 2007, and FDA observed violations during those inspections. In April 2012, FDA conducted another inspection of TABS RRC to determine if the IRB's activities and procedures for the protection of human

subjects complied with FDA regulations at 21 CFR parts 50 and 56. Following the 2012 inspection, FDA issued a Form FDA 483. On September 24, 2012, and after considering the IRB's response to the Form FDA 483, CBER issued to TABS RRC a Warning Letter/IRB Restrictions Letter (Warning Letter),¹ which cited multiple violations of 21 CFR part 56, the regulations governing the operations and responsibilities of IRBs, and which noted that one of the violations, the failure to maintain meeting minutes in accordance with 21 CFR 56.115(a)(2), was a repeat violation from the 2000 and 2007 inspections. In addition, pursuant to 21 CFR 56.120(b)(1) and (2), the Warning Letter placed restrictions upon TABS RRC until such time as FDA has evidence of adequate corrective actions and notifies TABS RRC in writing that its corrective actions are satisfactory. Specifically, CBER imposed the following restrictions as provided for in 21 CFR 56.120(b):

- (1) FDA will withhold approval of all new studies subject to 21 CFR Part 56 and reviewed by the IRB; and
- (2) No new subjects are to be enrolled in any ongoing studies subject to 21 CFR Part 56 and approved by the IRB.²

TABS RRC responded to the Warning Letter via letters dated October 8, 2012 and October 19, 2012. On January 18, 2013, CBER requested a Regulatory Meeting, and following the February 22, 2013 Regulatory Meeting, TABS RRC submitted responses dated March 18, 2013 and May 30, 2013 to FDA's request for additional documentation supporting TABS RRC's corrective action plans.³ On December 23, 2013, CBER sent a letter identifying violations cited in the Warning Letter for which the IRB had appropriately responded and for which CBER concluded the IRB had failed to provide adequate corrective actions. Although CBER requested

¹ Sept. 24, 2012 Warning Letter.

² *Id.* at 1, 5.

³ Jan. 18, 2013 Request for Regulatory Meeting from Center; March 18, 2013 TABS RRC Response and May 30, 2013 TABS RRC Response. *See also generally* Sept. 16, 2014 Notice of Opportunity for Hearing (NOOH) at 2.

that TABS RRC provide a response and include any documentation necessary to show that full and adequate correction has been achieved and although TABS RRC indicated in a December 23, 2013, email that it would respond, according to CBER, and as uncontested by TABS RRC, the IRB did not further respond to this letter.⁴

On September 16, 2014, the Associate Commissioner for Regulatory Affairs issued a Notice of Opportunity for Hearing (NOOH) Letter proposing the disqualification of TABS RRC. The notice asserted that TABS RRC had refused or repeatedly failed to comply with the regulations set forth in 21 CFR part 56 and that the non-compliance adversely affects the rights or welfare of human subjects in a clinical investigation.⁵ The NOOH also advised TABS RRC of its opportunity for a regulatory hearing under 21 CFR Parts 16 and 56. The NOOH was hand-delivered to Mildred Joyce Heinrich, the IRB's Chairperson.

On September 30, 2014, Ms. Heinrich submitted a letter on behalf of TABS RRC in which she waived the IRB's opportunity for a hearing.⁶ With regard to some matters set forth in the NOOH, TABS RRC submitted a letter purporting to provide corrective actions, explanations, and/or modified Standard Operating Procedures (SOPs). Subsequently, in March 2015, CBER submitted a Center Decision Memorandum to the Commissioner of Food and Drugs (Memorandum). As explained in the FDA Staff Manual Guide 7714, "Disqualification of an Institutional Review Board (IRB), Parent Institution, or Component of Parent Institution," which published prior to the IRB's September 30, 2014 response, if the IRB declined to request a hearing, the Center would then prepare a Center Decision Memorandum for the Commissioner

⁴ NOOH at 2-3; Dec. 23, 2013 CBER Follow up Letter to TABS RRC.

⁵ NOOH at 8-9.

⁶ See September 26, 2014 Response to the NOOH at 1 ("Pursuant to the Notice of Opportunity for Hearing (NOOH) letter I received September 16, 2014 I would like to waive my rights to a hearing with the FDA to further discuss the Warning Letter.").

and the Commissioner's counsel for review and decision. In the Memorandum, CBER asserts that TABS RRC refused or repeatedly failed to comply with the regulations set forth at 21 CFR part 56 and that this noncompliance adversely affects the rights or welfare of human subjects in a clinical investigation. Accordingly, CBER requests that the Commissioner sign an Order of Disqualification for TABS RRC pursuant to 21 CFR 56.121.⁷

The Memorandum included the following attachments:

- (1) Proposed Order of Disqualification for the Commissioner's signature;
- (2) Sept. 24, 2012 Warning Letter;
- (3) Oct. 8, 2012 TABS RRC Response to Warning Letter;
- (4) Oct. 19, 2012 TABS RRC Response to Warning Letter;
- (5) Nov. 8, 2012 Email from FDA Seattle District Office regarding NSR determination for (b) (4) ;
- (6) Nov. 14, 2012 TABS RRC Letter in response to Center request for information;
- (7) Jan. 18, 2013 Request for Regulatory Meeting from Center;
- (8) Mar. 18, 2013 TABS RRC Regulatory Meeting Response;
- (9) May 30, 2013 TABS RRC Regulatory Meeting Response;
- (10) Dec. 23, 2013 CBER Follow up Letter to TABS RRC;
- (11) Sept. 16, 2014 NOOH and proof of receipt;
- (12) Sept. 30, 2014 TABS IRB Response to the NOOH; and
- (13) Jan. 26, 2012 IRB Meeting Minutes.

⁷ Memorandum at 1, 8.

II. Analysis

A. The Standard for a Disqualification

Pursuant to 21 CFR 56.121(b):

The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

- (1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and
- (2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

As explained in the preamble to the final rule, “The important point is that the failure to comply is repeated and not an isolated event.”⁸ Decisions in the clinical investigator context have further expounded on the meaning of “repeated,” stating that a “Repeated Violation” means “a violation [that] occurred more than once. Violations are repeated even if they occur within one study.”⁹

Pursuant to 21 CFR 56.121(a), once disqualification proceedings have been initiated, an IRB is entitled to an opportunity for a part 16 regulatory hearing.¹⁰ Under 21 CFR 16.26(b), a hearing commences upon receipt by FDA of a request for a hearing under 21 CFR 16.22(b). Here, TABS RRC waived a hearing under part 16. If an IRB declines the opportunity for a hearing, the Commissioner will issue a decision, which may accept, in whole or in part, the findings of the Center regarding the alleged violations committed by the IRB and the conclusion that the IRB’s alleged noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

⁸ 46 Fed. Reg. 8958 at 8973 (Jan. 27, 1981).

⁹ See Commissioner’s Decision, In the Matter of Dr. Michael Dean Berger (June 20, 2014); see also FDA Staff Manual Guide 7714 “Disqualification of an Institutional Review Board (IRB), Parent Institution, or Component of Parent Institution” at 5 n.11 (collecting clinical investigator disqualification determinations defining the term “repeated”).

¹⁰ See also 21 CFR 16.22(a), 16.24(a).

Based on the record, I find that TABS RRC repeatedly failed to comply with 21 CFR part 56 and that the noncompliance adversely affects the rights or welfare of human subjects in a clinical investigation. For this reason, I am disqualifying TABS RRC under 21 CFR 56.121.

B. The IRB's Non-Compliance with 21 CFR Part 56.

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

Following an IRB inspection, FDA may send a letter to the IRB describing the noncompliance observed during the inspection, and, stating that until the IRB takes appropriate corrective action, FDA may impose certain restrictions on the IRB.¹¹ Here, in its September 24, 2012 Warning Letter, FDA informed TABS RRC that, pursuant to 21 CFR 56.120(b)(1) and (2), effective immediately, “FDA will withhold approval of all new studies” and that “[n]o new subjects are to be enrolled in any ongoing studies.” The Warning Letter further provided TABS RRC 15 business days to respond, and instructed the IRB to include in its response its communications with sponsors notifying them of the imposed restrictions.¹² In its responses to the Warning Letter, TABS RRC stated that it sent the sponsor and principal investigator for each ongoing clinical investigation a letter informing them of the restrictions imposed by FDA and included a list of sponsors and principal investigators to whom TABS RRC sent notification of the restrictions.¹³

CBER asserts that the study entitled (b) (4)

[REDACTED]

[REDACTED] and sponsored by (b) (4)

had been approved by TABS RRC and was ongoing at the time TABS RRC received the Warning

¹¹ 21 CFR 56.120(b).

¹² Warning Letter at 5-6.

¹³ Oct. 8, 2012 TABS RRC Response to Warning Letter at 32-45; Oct. 19, 2012 TABS RRC Response to Warning Letter at 18-24.

Letter. CBER states that the IRB failed to inform the sponsor of this study of the imposed restrictions and that 13 new study subjects were enrolled in the study after September 24, 2012.¹⁴

Although the IRB stated that it provided FDA with a list of sponsors and principal investigators for each ongoing clinical study and copies of letters sent to such entities informing them of the restrictions imposed, the (b) (4) study was not included in that list and no copies of letters sent to the (b) (4) sponsor or principal investigator were submitted. Additionally, in its response to the NOOH, TABS RRC did not contest CBER's allegations that the IRB had failed to notify (b) (4) of the restrictions imposed and that 13 new subjects were enrolled in the study subsequent to the IRB's receipt of the Warning Letter. TABS RRC thus both failed to adequately respond to the Warning Letter and to adhere to the restriction that "[n]o new subjects [] be enrolled in any ongoing studies." Therefore, based on the record before me, I find that TABS RRC failed to comply with the restrictions imposed in the September 24, 2012 Warning Letter, and, consequently, TABS RRC violated 21 CFR 56.120(b)(2).

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)).

Pursuant to 21 CFR 56.107(e), "[n]o 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."

CBER asserts that Ms. Heinrich and Dr. Martha Tripp, another IRB member, provided consulting services to (b) (4), which consisted of assisting (b) (4) in

¹⁴ NOOH at 3.

writing protocols and informed consent documents, and for which payment was requested. TABS RRC does not contest that Ms. Heinrich and Dr. Martha Tripp provided consulting services to (b) (4). In addition, according to the meeting minutes for the January 26, 2012 TABS RRC meeting, Ms. Heinrich and Dr. Tripp voted to approve three protocols sponsored by (b) (4).¹⁵

Based on the record before me, I find that TABS RRC violated 21 CFR 56.107(e). Ms. Heinrich and Dr. Tripp both had conflicts of interest. As noted above, CBER alleges and TABS RRC does not contest that Ms. Heinrich and Dr. Tripp provided consulting services to (b) (4) for which payment was requested. These relationships would reasonably be expected to undermine an IRB member's ability to exercise professional judgment and to provide an independent and impartial review of the (b) (4) protocols and are sufficient to create a conflict of interest. Indeed, although drafted after the January 26, 2012 meeting, the IRB's own SOP recognizes that these relationships would constitute conflicts of interest. Specifically, the SOP states that "[e]xamples of a conflicting interest" include where an IRB member is a "[m]ember of a Contract Research Organization (CRO) receiving funds (e.g., consulting fees or honoraria) from the study sponsor or investigator(s)."¹⁶ Moreover, the meeting minutes make clear that Ms. Heinrich and Dr. Tripp voted to approve the (b) (4) protocols. Therefore, I conclude that TABS RRC violated 21 CFR 56.107(e) because members participated in the initial or continuing review of a project in which such members had conflicts of interest.

TABS RRC further responded to CBER's allegations regarding its members' conflicts of interest by presenting an amended SOP addressing a member's duties to disclose conflicts of

¹⁵ Jan. 26, 2012 IRB Meeting Minutes at 2 (Page references for this exhibit are to the FEI: 300300814 Stamp). The minutes show that Dr. Tripp abstained from voting on one of the three (b) (4) protocols.

¹⁶ See Oct. 8, 2012 TABS Response to Warning Letter, SOP entitled "RRC Conflict of Interest" (Effective Date Sept. 15, 2012).

interest and to abstain from participation in reviewing, discussing, and voting on a project when that member has a conflicting interest. TABS RRC also informed CBER that Ms. Heinrich has been removed from the TABS RRC Membership Roster as a voting IRB member, and Dr. Tripp has been named as the Acting Chairperson. I will address these responses in Section II.D, below.

3. The IRB failed to fulfill membership requirements (21 CFR 56.107(a)).

Under 21 CFR 56.107(a), an IRB shall possess the professional competence necessary, among other things, to review specific research activities and to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. As explained in the preamble to the final rule, in order to allow flexibility in the make-up of the IRBs that review FDA-regulated research, every IRB is not required to include at least one physician. An IRB must nevertheless retain the necessary expertise to effectively review any protocol submitted to it and the preamble “emphasize[d] that § 56.107(a) requires that IRBs have *as members* persons with the professional competence necessary to review the proposed research. For example, FDA would expect that an IRB that reviews investigational new drug studies will include at least one physician.”¹⁷ In short, the final rule provides the IRB with flexibility to select its members where flexibility is warranted—it does not excuse an IRB from including individuals with relevant professional competence.

In the NOOH, CBER cites to three separate instances in which TABS RRC reviewed and approved studies without fulfilling membership requirements. Specifically, TABS RRC held meetings on January 8 and 26, 2012 and July 26, 2012, during which the IRB reviewed and approved an investigational device study involving both pediatric and adult subjects with

¹⁷ 46 Fed. Reg. at 8966 (emphasis added).

disorders of the (b) (4), an investigational device study involving subjects with (b) (4), and two studies involving the administration of

(b) (4) to patients with (b) (4)¹⁸ Using the (b) (4) studies as an example, the protocols for those studies state that the (b) (4)

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(b) (4)¹⁹ CBER maintains that, in each of those instances, the IRB did not include an individual with professional competence in the treatment of the respective disease or disorder (e.g., a physician).

In its response to the NOOH, TABS RRC does not dispute that its IRB membership did not include an individual with professional competence in the treatment of the diseases and disorders identified above (e.g., a physician) during the time when the above protocols were reviewed. Quite to the contrary, the IRB “acknowledge[d] the FDA’s concern stated . . . above relative to the lack of professional competence to review and address clinical protocols” and answered the allegations in the NOOH by claiming that its Medical Advisory Board had the relevant professional competence. Nevertheless, as conceded by the IRB, those individuals are *non-voting*²⁰—i.e., they are not “members” of the IRB.²¹ In addition, TABS RRC claims that it consulted with a (b) (4) expert, an assertion the IRB supports by citation to meeting minutes

¹⁸ NOOH at 5-6; Oct. 8, 2012 TABS RRC Response to Warning Letter at 70-73; Jan. 26, 2012 IRB Meeting Minutes.

¹⁹ Jan. 26, 2012 IRB Meeting Minutes at 43; *see also id.* at 11.

²⁰ Sept. 30, 2014 TABS IRB Response to the NOOH at 5-7.

²¹ *See* 46 Fed. Reg. at 8966 (rejecting a comment that “consultants be allowed to vote with an IRB” because “[t]he decision of an IRB must represent the judgment of the members of the IRB. Although consultants should provide information about the ethical acceptability of a study, FDA believes it would be a distortion of their function to permit them to vote.”).

stating that “Additional information was sought from an external source that had extensive background in (b) (4) research.” and by its notes from that consultation.²²

Based on the record before me, I concur with CBER’s conclusion that the members of TABS RRC did not have sufficient professional competence to review the investigations described above, and I therefore find that TABS RRC repeatedly violated 21 CFR 56.107(a). Specifically, considering the nature of those trials, including the investigational products under study, the diseases or conditions being studied, the inclusion of pediatric subjects in one of the trials, and the nature of review expected pursuant to part 56,²³ under 21 CFR 56.107(a), it was necessary for TABS RRC to include individuals with professional competence (*e.g.*, a physician) in the treatment of the diseases and disorders under study as *actual members* of the IRB and that none of TABS RRC’s members who participated in the January 8 and 26, 2012 and July 26, 2012 meetings had such professional competence.

In addition, I find TABS RRC’s assertion that it could cure its lack of professional competence through consultations unavailing. Rather, as emphasized in the preamble, § 56.107(a) requires that IRBs have “as members” persons with the professional competence necessary to review the proposed research. Nevertheless, even if I were to accept that the IRB could ameliorate the violation described above via consultations, I find the consultations here to

²² Jan. 26, 2012 IRB Meeting Minutes at 2; Oct. 19, 2012 TABS RRC Response to Warning Letter at 3-7; Oct. 8, 2012 TABS RRC Response to Warning Letter at 19-21.

²³ In addition to the standard set forth in 21 CFR 56.107(a), the criteria to approve research activities require the IRB to determine, among other things, that there are adequate provisions for monitoring the data collected to ensure the safety of subjects; that risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk; that risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects; and the importance of the knowledge that may be expected to result. *See* 21 CFR 56.111(a). *See also* 46 Fed. Reg. at 8961-62 (Although an IRB is not tasked with primary scientific review responsibilities for clinical studies, the IRB is obligated “to assure that a review of the scientific merits of a proposal is conducted,” and an IRB “cannot reasonably review a study or make a valid risk assessment, unless there has been a positive assessment of the scientific merits of the research.”).

be insufficient.²⁴ According to the IRB, its consultation with a “core group of medical advisors” provided adequate assistance in its review.²⁵ Nevertheless, TABS RRC fails to explain what type of competency the “core group of medical advisors” possessed or how the knowledge and experience of these *non-member* advisors impacted the IRB’s review and ultimate approval of the protocols. In addition, TABS RRC contends that its consultation with an individual with “extensive experience in (b) (4) research” ensured adequate competence in the review and approval of the (b) (4) studies on January 26, 2012. Notwithstanding this statement, however, the IRB failed to demonstrate that the consultation provided any relevant expertise—let alone expertise that could have cured the IRB’s lack of competence. The meeting minutes only state that information was “sought” from a third-party, with no description of what type of information was sought or even whether it was ultimately received prior to the January 26, 2012 meeting approving the studies. Moreover, the notes documenting consultations that the IRB did submit were dated February 1, February 8, and February 16, 2012²⁶—all of which are *after* the IRB approved the (b) (4) studies. Consequently, even if TABS RRC could have resolved its lack of professional competence by reliance on outside experts, its consultation was not sufficient in this instance.

Finally, in its response to the NOOH, TABS RRC provided a revised SOP dated February 2014 to show that TABS RRC has added a medical doctor to its membership roster.²⁷ I will address this issue in Section II.D. below.

²⁴ According to 21 CFR 56.107(f), “an IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB.” Section 56.107(f), however, does not vitiate the requirement in § 56.107(a) that an IRB’s *members* must have professional competence. *See supra* n. 17.

²⁵ *See* Oct. 8, 2012 TABS RRC Response to Warning Letter at 17.

²⁶ *See* Oct. 8, 2012 TABS RRC Response to Warning Letter at 19-21; Oct. 19, 2012 TABS RRC Response to Warning Letter at 1.

²⁷ *See* Sept.30, 2014 TABS IRB Response to the NOOH at 5, Attachment I.

4. The IRB failed to prepare and maintain adequate documentation of IRB activities (21 CFR 56.115).

Under 21 CFR 56.115(a)(2), an IRB shall maintain adequate documentation of its activities, including minutes of IRB meetings which shall be in sufficient detail to show attendance at 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. CBER asserts that the failure to maintain meeting minutes had also been identified in FDA inspections of TABS RRC in 2000 and 2007²⁸—an assertion that TABS RRC does not dispute.

CBER charges that TABS RRC did not maintain meeting minutes for 2011. Specifically, according to CBER, the IRB's study list shows that protocol TABS (b) (4) was modified and approved on August 24, 2011, and, in addition, the FDA investigator was informed that the IRB met twice in 2011. However, there were no meeting minutes available for 2011.

With respect to the August 24, 2011 meeting, TABS RRC does not dispute CBER's statement that the protocol TABS (b) (4) was modified and approved on August 24, 2011, and the record before me does not include any meeting minutes for that date. Accordingly, I find that TABS RRC violated 21 CFR 56.115(a)(2) by failing to maintain meeting minutes for the August 24, 2011 meeting.

In addition, with respect to the two other meetings, TABS RRC submitted meeting minutes dated May 26, 2011 and August 18, 2011 in response to the September 24, 2011 Warning Letter.²⁹ The IRB does not dispute that these meeting minutes were not available during the April 2012 inspection. According to CBER, during the inspection, TABS RRC

²⁸ NOOH at 6; Oct. 19, 2012 TABS RRC Response to Warning Letter at Att. 2.

²⁹ Oct. 19, 2012 TABS RRC Response to Warning Letter at Att. 2.

explained to the FDA investigator that, due to a computer crash, all minutes and data from 2011 were lost. TABS RRC later offered to re-create meeting minutes from handwritten notes.

Although CBER requested that TABS RRC submit the handwritten notes rather than re-create a typed version of the lost minutes, the IRB submitted typed notes of May 26, 2011 and August 18, 2011 meetings. Consequently, according to CBER, the minutes submitted in response to the Warning Letter are not contemporaneous minutes, but rather, recreations of the missing minutes.³⁰ On the other hand, TABS RRC states that while the “minutes from two meetings in 2011 were lost due to computer crash and were unavailable for review by the FDA investigator as stated at the time of the FDA inspection,” it could and did retrieve electronic and handwritten minutes from its off-site archives.³¹ Specifically TABS asserts that, when it offered to “re-create” the meeting minutes, the IRB intended to retrieve all handwritten and electronic minutes from its off-site archived files and organize the minutes to document the flow of discussions.³²

I find that TABS RRC’s explanation regarding the May 26, 2011 and August 18, 2011 meetings strains credibility. I have reviewed the purported meeting minutes that TABS RRC asserts it retrieved from its off-site storage facility, both of which were extremely cursory and conclusory. According to the minutes for the May 26, 2011 meeting, the IRB reviewed and approved the Principal Investigator (PI) applications for three individuals; however, the minutes include no discussion of the PIs’ qualifications and include no attached documentation of their credentials.³³ On August 18, 2011, the IRB met to review two modifications to the (b) (4)

protocol, including removing two of the exclusion criteria from the original protocol. The

³⁰ NOOH at 6; Memorandum at 6.

³¹ Sept. 30, 2014 TABS IRB Response to the NOOH at 8; Oct. 8, 2012 TABS RRC Response to Warning Letter at 27; Oct. 19, 2012 TABS RRC Response to Warning Letter at Att. 2. TABS RRC also includes an SOP revised in April 2014 to reflect an upgraded meeting minutes storage process. See Sept. 30, 2014 TABS IRB Response to the NOOH at 8 & Att. III; Memorandum at 6-7.

³² Oct. 8, 2012 TABS RRC Response to Warning Letter at 27.

³³ Oct. 19, 2012 TABS RRC Response to Warning Letter at Att. 2.

complete summary of the IRB’s discussion of this issue is as follows, “**Modification to Study Population Exclusion Criteria** – Remove 2 of the exclusion criteria from original protocol as justified in (b) (4) letter. Unanimous agreement of IRB.”³⁴

In addition, I further note the significant delay in TABS RRC’s offer to “re-create” the minutes—an offer clearly divergent from its initial statement that the minutes were lost—and the ultimate provision of the purported meeting minutes to FDA. The inspection occurred in April 2012, and the IRB does not dispute CBER’s assertion that TABS RRC informed the FDA inspector at that time that the 2011 meeting minutes were lost due to a computer crash. Moreover, during an April 26, 2012 meeting, the IRB acknowledged that FDA issued a Form 483, which “revolved primarily around,” *inter alia*, “documentation of the Committee’s meeting minutes,” and Ms. Heinrich indicated that “she would reply in writing . . . to each observation cited,” including providing additional SOPs where necessary.³⁵ No mention was made that the meeting minutes could be “re-created” or were potentially available at an off-site archive. Indeed, it was not until a September 27, 2012 teleconference that the IRB first offered to re-create the minutes and not until October 19, 2012 that the IRB first presented the meeting minutes allegedly retrieved from the archives to FDA.

Based on the extremely cursory and conclusory nature of the minutes provided by TABS RRC—especially the summary of the discussion regarding the changes to the (b) (4) protocol—and the delay in informing FDA that the meeting minutes could even be “re-created” or retrieved and ultimately providing the meeting minutes to FDA, I find that the meeting minutes were likely recreated, as CBER maintains, and were not drafted contemporaneously,

³⁴ Oct. 19, 2012 TABS RRC Response to Warning Letter at Att. 2 (emphasis in original). (b) (4) letter provides a one-sentence justification – specifically, the letter requests the change because patients with previous therapy and with (b) (4). *Id.*

³⁵ Oct. 8, 2012 TABS RRC Response to Warning Letter at 49 (Attachment VIII, Meeting Minutes from 2012).

only to be retrieved from an off-site archives, as the IRB asserts. Accordingly, I find that TABS RRC failed to maintain minutes for the May 26, 2011 and August 18, 2011 meetings.^{36 37}

5. The IRB Repeatedly Violated 21 CFR Part 56.

Based on the foregoing, I conclude that the IRB violated the following sections of part 56: 21 CFR 56.120(b)(2) (failure to adhere to restrictions imposed); 21 CFR 56.107(e) (failure to ensure no member participated in the review of a project in which the member had a conflict of interest); 21 CFR 56.107(a) (failure to fulfill membership requirements); and 21 CFR 56.115(a)(2) (failure to prepare and maintain adequate documentation of IRB activities).³⁸

Given the multiple violations described above, I find that the first prong of the disqualification standard is met—*i.e.*, that TABS RRC has repeatedly failed to comply with the part 56 regulations.³⁹

³⁶ The “preponderance of the evidence” is the correct standard to apply to IRB disqualifications. *Cf.* Commissioner’s Decision, In the Matter of Huibert M. Vriesendorp (2001) (finding that “the ‘preponderance of the evidence’ standard applies in clinical investigator disqualification hearings”); Commissioner’s Decision, In the Matter of Paul W. Boyles (1995) (“The Center has the burden of establishing the alleged violations by the preponderance of the evidence” in clinical investigator disqualifications).

³⁷ Although the NOOH included an alleged violation related to the records for the (b) (4) study, CBER does not assert this violation in its Memorandum. Therefore, I do not address it here.

³⁸ In the NOOH and the Center Memorandum, CBER asserts that a meeting held by TABS RRC on November 7, 2012, during which TABS RRC allegedly conducted a Nonsignificant Risk (NSR) determination, violated multiple provisions in part 56. *See* NOOH at 4; Center Memorandum at 5 (alleged violation of 21 CFR 56.107(e)); NOOH at 6-7; Center Memorandum at 6-7 (alleged violation of 21 CFR 56.115); and NOOH at 7-8; Center Memorandum at 7-8 (alleged violation of 21 CFR 56.108(a) and 56.115(a)(6)). An IRB’s conduct while making an NSR or significant risk (SR) determination in connection with a device to be used in clinical investigations is subject to part 56. According to 21 CFR 812.60, “An IRB reviewing and approving investigations under this part [part 812] shall comply with the requirements of part 56 in all respects, including its composition, duties, and functions,” and a determination of nonsignificant risk is under 21 CFR 812.66. *See also* Medical Devices; Procedures for Investigational Device Exemptions, 45 Fed. Reg. 3732 (Jan. 18, 1980) (preamble to final rule) at 3736 (“FDA has concluded that the protection of human subjects is not fostered by requiring a sponsor to submit an application to FDA for approval before commencing an investigation of a nonsignificant risk device. Protection of the public health and safety and the application of community-based ethical standards are adequately assured by the role of IRB’s in reviewing such investigations.”); *id.* at 3747 (“[A]n IRB collectively must be able to evaluate the risks and scientific soundness of proposed investigations in order to determine, for example, that the investigation is not disguised quackery or clearly will not yield useful results. In particular, an IRB must be able to review carefully and critically a sponsor’s characterization of an investigational device as not presenting a significant risk.”). Nevertheless, given the lack of clarity in the record, and given that I find that disqualification is warranted based on other violations, I need not address CBER’s allegations relating to the November 7, 2012 meeting.

³⁹ 21 CFR 56.121(b)(1).

C. The Violations of TABS RRC Adversely Affect the Rights or Welfare of the Subjects.

I next address whether TABS RRC's non-compliance adversely affects the rights or welfare of human subjects under 21 CFR 56.121(b)(2). The preambles to this regulation do not provide specific guidance as to when a particular violation may adversely affect the rights and welfare of human subjects. Accordingly, in addressing this issue, I have carefully considered, among other things, the fundamental ethical principles and recommendations set forth in two publications of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Commission): "Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research" (Belmont Report) and "Institutional Review Boards: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research," (IRB Report and Recommendations) in which the Commission set forth recommendations for regulations to be promulgated by the Department of Health and Human Services (HHS).⁴⁰

1. The Role of the IRB in Providing Third-Party Oversight.

The Belmont Report discussed the importance of distinguishing between biomedical research and the practice of accepted therapy and concluded that "if there is any element of research in an activity, that activity should undergo review for the protection of human

⁴⁰ Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 44 Fed. Reg. 23192 (Apr. 18, 1979); Institutional Review Boards: Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 43 Fed. Reg. 56174 (Nov. 30, 1978). The Commission was established, *inter alia*, to develop ethical guidelines underlying the conduct of research involving human subjects. See Pub. L. No. 93-348 Sec. 202(a)(1)(A). Following issuance of the Report and Recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, FDA issued a revised proposal to part 56 to ensure compatibility with revisions to HHS regulations made in response to the Commission's recommendations. In addition, ethicists and IRBs today continue to weigh the three fundamental ethical principles set forth in the Belmont Report.

subjects.”⁴¹ The Commission echoed this sentiment in its IRB Report and Recommendations where it stated, “The Commission’s deliberations begin with the premise that investigators should not have sole responsibility for determining whether research involving human subjects fulfills ethical standards. Others, who are independent of the research, must share this responsibility, because investigators are always in positions of potential conflict by virtue of their concern with the pursuit of knowledge as well as the welfare of the human subjects of their research.”⁴² Thus, IRBs play an essential role in the protection of human subjects and IRB review of proposed research “is the *primary mechanism* for assuring that the rights of human subjects are protected.”⁴³

The Belmont Report discussed and applied fundamental ethical principles of relevance to research on human subjects. I discuss two of these principles here: 1) the ethical principle of beneficence, which as applied to human research, forms the basis of the requirement of independent review of risks and potential benefits and 2) ethical the principle of respect for persons, which as applied to human research, forms the basis of the requirement of informed consent.⁴⁴

⁴¹ Belmont Report, 44 Fed. Reg. at 23193.

⁴² 43 Fed. Reg. at 56175. *See also id.* at 56183 (In its IRB Report and Recommendations, the Commission reasoned that ethical principles will require interpretation when applied to specific situations: “In research involving human subjects, the desirability of bringing to bear on such interpretations the judgment of individuals other than the research investigator has come to be widely recognized and is the basis of present regulatory approaches to the protection of human subjects.”); *id.* at 35186 (As explained in the August 8, 1978 preamble to part 56, “The benefits of institutional review include . . . independence from competing interests.”). FDA withdrew its August 8, 1978, proposal to incorporate the recommendations set forth by the Commission on November 30, 1978. However, FDA explained that, to the extent that its re-proposal was not changed from the earlier proposal, the agency incorporated the August 8, 1978 preamble. Further, FDA retained its August 8, 1978, proposal regarding the disqualification of IRBs. 44 Fed. Reg. 47688 at 47699-47700, 47702 (Aug. 14, 1979).

⁴³ 43 Fed. Reg. at 56714 (emphasis added), 56716; *see also* 21 CFR 56.101(a) (“Compliance with this part is intended to protect the rights and welfare of human subjects.”).

⁴⁴ Belmont Report, 44 Fed. Reg. at 23193-195. The Commission applied the third ethical principle – justice – to the selection of subjects. *Id.* at 23196-97. Given that none of the IRB’s violations of part 56 involved the selection of subjects, this principle is not discussed here.

a. The Role of the IRB in Implementing the Ethical Principle of Beneficence.

The basic ethical principle of beneficence is understood as an obligation to protect people from harm and to maximize possible benefits and minimize possible harms.⁴⁵ Applying the principle of beneficence to review committees, the assessment of risks and benefits is a method of determining whether the risks presented to subjects are justified.⁴⁶ The Belmont Report recommended that the review of risks should be systematic and nonarbitrary as much as possible, which requires decision-makers to be thorough in the accumulation and assessment of information about the research and to consider alternatives systematically. An assessment of the justifiability of research should assess whether the risks are reduced to those necessary to achieve the research objective.⁴⁷

The Commission recommended that the regulations require IRB approval to be based upon affirmative determinations including: that the research methods are appropriate to the objectives of the research; that the risks to subjects are minimized by using the safest procedures consistent with sound research design; and that risks are reasonable in relation to anticipated benefits to subjects and the importance of the knowledge to be gained.⁴⁸ As in the Belmont Report, the Commission emphasized the need for a systematic analysis of the risks and benefits of human research and further noted that, “As risk increases and, similarly, as the vulnerability of patients increases (by virtue of illness, institutionalization, etc.), it becomes more important to

⁴⁵ *Id.* at 23194.

⁴⁶ *Id.* at 23196.

⁴⁷ *Id.* at 23196.

⁴⁸ 43 Fed. Reg. at 56179.

evaluate risks of harm and possible benefits and to require a reasonable relation between them.”⁴⁹

b. The Role of the IRB in Implementing the Ethical Principle of Respect for Persons.

A second basic ethical principle set forth in the Belmont Report as being of particular relevance here is the principle of respect for persons. This principle requires that individuals (except for those with diminished autonomy) be treated as autonomous agents, and respect for autonomy requires giving weight to an individual’s considered opinions and choices.⁵⁰

“[R]espect for persons demands that subjects enter into the research voluntarily and with adequate information.”⁵¹ A lack of respect for autonomy would include withholding “information necessary to make a considered judgment, when there are no compelling reasons to do so.”⁵² As applied to the conduct of research, respect for persons requires that subjects who are capable “be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.”⁵³

Consistent with the ethical principle of respect for persons, the Commission recommended that approval of research be based on a finding that informed consent will communicate to subjects information that subjects may reasonably be expected to want to know in considering whether or not to participate in the research, including any foreseeable risks to subjects.⁵⁴

⁴⁹ *Id.* at 56180.

⁵⁰ Belmont Report, 44 Fed. Reg. at 23193.

⁵¹ *Id.* at 23194.

⁵² *Id.* at 23193.

⁵³ *Id.* at 23195.

⁵⁴ *Id.* at 56179.

2. The IRB’s Violations of 21 CFR 56.107(a) and (e) Adversely Affect the Rights or Welfare of Human Subjects.

a. Violation of 21 CFR 56.107(a).

The IRB’s violation of 21 CFR 56.107(a)—the failure to fulfill IRB membership requirements—adversely affects the rights or welfare of human subjects.

As described above, *supra*, Section II.B.3, TABS RRC reviewed an investigational device study involving both pediatric and adult subjects with disorders of the (b) (4)

, an investigational device study involving subjects with (b) (4)

, and two studies involving the administration of (b) (4) to patients with

(b) (4)⁵⁵ Given the nature of the diseases, the products to be studied, and the vulnerable patient populations, the IRB membership required the training and expertise of a voting individual with professional competence in the treatment of these diseases and disorders (*e.g.*, a physician).

Review by a third party which is independent from the research is critical to an IRB’s fundamental objective of protecting the rights and welfare of human subjects. Here, the purpose of third party oversight could only be achieved if the third party reviewing the studies possessed an understanding of the etiology and progression of each disease or condition, the benefits and risks of the standard of care and approved treatments for each disease or condition, and the current body of scientific knowledge regarding each disease or condition. Indeed such an understanding would be necessary for an IRB to fulfill its duty to adequately consider the risks and benefits of the research (as distinguished from the risks and benefits of therapies patients with these diseases and conditions would receive outside of a clinical investigation), to determine

⁵⁵ NOOH at 5-6; Oct. 8, 2012 TABS RRC Response to Warning Letter at 70-73; Jan. 26, 2012 IRB Meeting Minutes.

whether the risks to human subjects are reasonable in relation to the potential benefits of the research, and to evaluate the acceptability of the proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.⁵⁶ Given that the IRB lacked the competence to review these studies, the IRB could not fulfill one of the fundamental purposes of third party oversight of clinical research, namely completion of an adequate evaluation of the research, which adversely affects the rights or welfare of the human subjects.

In addition, because TABS RRC did not possess the professional competence necessary to evaluate the risks and benefits of these protocols, it follows that the IRB was unable to ensure the adequacy of informed consent, particularly with regard to the risks and benefits of the trials. The basic ethical principle of respect for persons demands that subjects enter into research voluntarily and with adequate information, and, as a result of its lack of professional competence, TABS RRC failed to fulfill this ethical duty.

b. Violation of 21 CFR 56.107(e).

The IRB's violation of 21 CFR 56.107(e)—the failure to ensure that no member participates in the review of a project in which such member has a conflicting interest—adversely affects the rights or welfare of human subjects.

As explained above, IRB review is founded on the principle that the protection of human subjects must not depend solely upon investigators alone because investigators are always in a potential conflict of interest. Indeed, 21 CFR 56.107(e) is intended to protect the independence

⁵⁶ See 21 CFR 56.107(a); 56.111(a).

and objectivity of the IRB.⁵⁷ Where, as here, TABS RRC was also conflicted with regard to the (b) (4) trial, its review of the trial failed to achieve the fundamental purpose of IRB review.

A conflict would reasonably be expected to influence an IRB member's judgment and objectivity resulting in the conflicted IRB member projecting an unbalanced view of the benefits and risks of the study, downplaying the possible risks and promoting the possible benefits, thus leaving the protection of the human subjects in these trials to the investigators alone. This result adversely affected the rights or welfare of the human subjects in those trials.

Moreover, where a conflict may impact an IRB member's objectivity, leading that member to project a biased view of the benefits and risks of a trial, the conflict may also influence the IRB's discussion of the informed consent for that trial. Thus, there is not sufficient assurance that the subjects received adequate and accurate information about the risks and benefits of the proposed studies.

c. Application to the (b) (4) Trials.

The implications of these violations on the rights or welfare of human subjects are illustrated by the IRB's review of the (b) (4) protocol and informed consent form for the (b) (4)

⁵⁸ The consequences of these violations are further heightened for the (b) (4) trials, given the serious nature of the diseases and conditions to be studied and the significant vulnerability of subjects with such diseases.

As described above, the January 26, 2012 review of the (b) (4) trials was conducted with an IRB that lacked the required professional competence (*e.g.*, a physician). In addition,

⁵⁷ 43 Fed. Reg. at 35191.

⁵⁸ A comment bubble inserted into the Jan. 26, 2012 IRB Meeting Minutes at 19 suggests that this protocol involved only data collection. However, a review of the content of the protocol confirms that this is intended to be a study of the safety and efficacy of (b) (4).

two members of the IRB participated in the review of the (b) (4) protocols despite those members having provided consulting services to (b) (4) for which payment was requested. Both the lack of professional competence and the business relationship between the two IRB members and (b) (4) would be expected to compromise the impartiality and objectivity of the IRB, thereby vitiating the IRB's critical, third-party reviewer role and undermining its ability to protect the rights and welfare of human subjects. As described in more detail below, these violations adversely affected the rights or welfare of the human subjects enrolled in the (b) (4) clinical investigation.

TABS RRC's review of the (b) (4) protocols violated the principle of beneficence, as the IRB voted to approve the protocols, even though its review of the protocols noted significant deficiencies. According to the meeting minutes, TABS RRC members observed that the inclusion criteria for the research are very broad and recommended that the "actual number of diseases or conditions be limited initially." In addition, the IRB members noted that the protocol lacked sufficient detail in its descriptions of the treatment procedure, the methods for (b) (4) and administration to subjects, and the monitoring of subjects. Furthermore, as described in the meeting minutes, additional clarification and input was required from the sponsor.⁵⁹ Nonetheless, despite the unavailability of such information deemed by the IRB to be necessary, TABS RRC voted unanimously to approve these studies.

The deficiencies TABS RRC observed regarding the description of the treatment procedure, (b) (4), and monitoring of subjects directly impact the welfare of human subjects in those trials. Without a sufficient description of the treatment procedure, the methods for (b) (4) and administration, and monitoring, TABS RRC *could not know* the risks of

⁵⁹ Jan. 26, 2012 IRB Meeting Minutes at 2-3.

this procedure and could not begin to undertake an adequate risk-benefit analysis. Moreover, the broad inclusion criteria and the lack of clear objectives for this study raise significant questions regarding the knowledge, if any, to be gleaned from the study. Where, as here, the IRB observed that such fundamental changes to the protocol were needed, and where those changes directly impact the risk-benefit analysis, TABS RRC's vote to approve these studies without first reviewing the changes made to the protocol in response to its comments adversely affects the rights or welfare of the subjects in the clinical investigation.⁶⁰

In addition, the IRB also failed to ensure adequate informed consent. The basic elements of informed consent include a description of any reasonably foreseeable risks or discomforts to the subject.⁶¹ Here, the protocol stated that the administration of (b) (4) posed a greater than minimal risk and that risks may include (b) (4)

[REDACTED]

[REDACTED]

[REDACTED] However, the informed consent form only stated, (b) (4)

[REDACTED] In other words, the informed consent form listed only the risks of the (b) (4) and failed to describe the risks of the

(b) (4). At minimum, this issue warranted discussion prior to TABS RRC's approval of these protocols. There is nothing in the meeting minutes to indicate that TABS RRC discussed this

⁶⁰ The fact that TABS RRC's approval of the (b) (4) trials was unanimous does not alter my conclusion. Because of the conflicts of two of the (b) (4) members present at the January 26, 2012 meeting would be expected to influence the discussion among all of the IRB members, and, in addition, the IRB lacked the professional competence to review the protocols, I do not find that the unanimous votes here offer adequate assurance that the rights or welfare of human subjects in the (b) (4) trials were protected.

⁶¹ See 21 CFR 50.25(a)(2). Under 21 CFR 56.111(a)(4), the criteria for IRB approval of research include a finding that informed consent will be sought from each subject in accordance with 21 CFR part 50.

⁶² Jan. 26, 2012 IRB Meeting Minutes at 15.

⁶³ *Id.* at 19.

issue or the basis for the IRB's conclusion that the informed consent form adequately satisfied the elements of informed consent set forth in 21 CFR 50.25(a).

On the basis of these violations alone, in light of the foregoing analysis, I find that the second criterion for disqualification is met. Therefore, I find that disqualification under 21 CFR 56.121(b) is warranted.

3. Other Violations of Part 56.

While the analysis described above is sufficient to find that the requirements of 21 CFR 56.121(b) are met and disqualification is warranted, my conclusion is further supported by the adverse effects on the rights or welfare of human subjects stemming from the IRB's failure to comply with the restrictions imposed by FDA in the September 24, 2012 Warning Letter.

The IRB's failure to adhere to the restrictions imposed also adversely affected the rights or welfare of human subjects. The September 24, 2012 Warning Letter informed TABS RRC that "[n]o new subjects are to be enrolled in any ongoing studies subject to 21 CFR part 56 and approved by the IRB." The Warning Letter further directed the IRB to notify each of the affected sponsors and clinical investigators of the imposed restrictions. In its October 8, 2012 response, TABS RRC stated that it "has written a letter and sent it to each Sponsor & Principal Investigator for each ongoing clinical investigational protocol." The IRB also included a copy of each notification letter with its response.⁶⁴ Notwithstanding its statements to CBER, TABS RRC failed to inform the sponsor of the (b) (4) study of the imposed restrictions, and, as a result, 13 new patients were enrolled.

⁶⁴ Oct. 8, 2012 TABS RRC Response to Warning Letter at 32-45. In its October 19, 2012 Response to CBER, TABS RRC included a letter to another sponsor, which was inadvertently omitted from the October 8, 2012 Response. See Oct. 19, 2012 TABS RRC Response to Warning Letter at 1.

The failure of TABS RRC to notify the sponsor of the (b) (4) study indicates a fundamental flaw in the IRB's ability to account for the studies for which it had ongoing oversight responsibilities under 21 CFR 56.109(f). Continuing oversight is not limited to receiving reports of unanticipated problems involving risk to subjects. Regarding continuing oversight, FDA has explained that "[a]ny action or failure to act during the investigation that adversely affects the ability of the investigation to yield these benefits [to the subjects and to scientific knowledge] may, as a consequence destroy the justification for the risk. Further exposure of humans may no longer be warranted."⁶⁵ Because it appears that TABS RRC had no knowledge that the (b) (4) study was ongoing, there is no confidence that the IRB was completing its continuing oversight of research. Therefore, the subjects in the (b) (4) clinical trial were participating with a false assurance that an IRB was performing continuing oversight of the research. As with the violations discussed above, the IRB's failure to comply with the restrictions imposed results in the investigators having the sole responsibility for the rights and welfare of the human subjects in the (b) (4) trial, at least with regard to continuing oversight. Accordingly, I conclude that TABS RRC's failure to comply with the restrictions imposed adversely affected the rights or welfare of human subjects.

Finally, while I do not make a finding as to whether the IRB's failure to prepare and maintain adequate documentation adversely affects the rights or welfare of human subjects, I note that the records an IRB is required to maintain "provide significant evidence of whether the procedures utilized by the IRB are adequately protecting the human subjects of the investigations

⁶⁵ 43 Fed. Reg. at 35188 (FDA also explained that continuing review provides for conformity with the approved protocol and enhances protection of subjects by assuring that any changes in protocols are reviewed and approved in advance.).

the IRB is reviewing.”⁶⁶ TABS RRC has a lengthy history of non-compliance dating to 2000, and the IRB’s failure to retain required documents undermines FDA’s ability to determine whether the IRB complied with part 56.

D. The IRB’s Discussion of its Efforts to Address Certain Violations is Inadequate.

Under 21 CFR 56.121, to conclude that disqualification is appropriate, I am only required to find that TABS RRC has repeatedly violated part 56 and that those violations adversely affect the rights and welfare of the human subjects in a clinical investigation. 21 CFR 56.121(b). Nonetheless, I have considered the fact that TABS RRC has taken steps to address certain violations, including the addition of a physician as a member, the appointment of a new Acting Chairperson, and the development of new SOPs, and I find these steps do not overcome the repeated and chronic violative actions of the IRB that form the basis for my disqualification determination. The IRB has repeatedly failed to follow FDA’s regulations and its own procedures, and as a result, the new SOPs offer little assurance that TABS RRC will comply with part 56 in the future. In addition, while the IRB appointed Dr. Tripp as new Acting Chairperson, she had conflicts in the review of the (b) (4) trials as a result of her consulting work for (b) (4). Therefore, I have little assurance that Dr. Tripp will refrain from review of a project in which she has a conflicting interest.

My conclusion is reinforced by the very serious nature of the violations, particularly the violations related to the IRB’s competence and the conflicts of interest and the failure to comply with the restrictions imposed. I have discussed at length how these violations adversely affect the rights or welfare of human subjects, and the implications of the violations on the review of the (b) (4) protocols and informed consent. The record also evidences TABS RRC’s inability

⁶⁶ 46 Fed. Reg. at 8970.

to understand fundamental issues related to the duties of an IRB, including the IRB's vote to approve the (b) (4) trials despite the significant issues raised during its review.

Finally, in the related context of clinical investigator disqualifications, I note that the provision of "adequate assurances" of future compliance cannot avoid disqualification. Indeed, when FDA issued the final rule, it explained in the preamble that the final version "deletes the provision [in the current standards and procedures governing disqualification] allowing a clinical investigator to avoid disqualifications through the submission of 'adequate assurances' of future compliance."⁶⁷ Rather, "adequate assurances" are properly considered outside the context of the disqualification proceeding and are relevant to the reinstatement process.⁶⁸

III. Conclusion

For the reasons set forth above, and upon consideration of the record as a whole, I find that the requirements for disqualification are met: TABS RRC has repeatedly violated the requirements of 21 CFR part 56, and TABS RRC's noncompliance adversely affects the rights or welfare of human subjects in a clinical investigation. This finding is consistent with the preamble's counsel that disqualification is generally reserved for "extraordinary circumstances."⁶⁹ Accordingly, TABS RRC is disqualified pursuant to 21 CFR 56.121(b). TABS RRC may seek reinstatement under 21 CFR 56.123.

⁶⁷ See 52 Fed. Reg. 8798 at 8826 (1987) (preamble to final New Drug, Antibiotic, and Biologic Drug Product Regulations).

⁶⁸ *Id.*; see also 21 CFR 312.107(f) ("An investigator who has been determined to be ineligible to receive investigational drugs may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances . . ."). Reinstatement of a disqualified IRB similarly requires the presentation of "adequate assurances." 21 CFR 56.123 ("An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part.").

⁶⁹ In the preamble to part 56, FDA stated that "[d]isqualification will be used by the agency only when it is necessary to protect the rights and welfare of human subjects, and after the institution or IRB has refused or has continuously failed to comply with these regulations. . . . [T]he agency does not expect to use this sanction except in the most extraordinary circumstances." 43 Fed. Reg. at 8973.

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Dated: February 29, 2016.