November 30, 2009

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Acting Human Subjects Protections Team Lead
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 51, Room 5356
Dear Dr.Prohaska:

I am Chairman of the BRI IRB and I am writing in response to the FDA's Warning letter of October 5, 2009. This response incorporates suggestions made in a conference call with the FDA on November 5, 2009. I will first address some of the general deficiencies noted and then discuss the deficiencies and observations regarding the specific studies addressed in the FDA's October 5th communication.

We acknowledge that the minutes of some of the meetings are unclear and in some instances do not clearly delineate the study or protocol which is the subject of the discussion documented by the mintues In addition, in the past, the transcription of the record of the voting was always clear, and sometimes did not correctly reflect that, for example in the case of conflict of interests, the person with the conflict did not vote.

Now that we have been made aware of these issues, we will make sure that the minutes are clearer and more accurately reflect what has transpired in our meetings. In addition, in the future, the minutes will specifically note that anyone with a conflict of interest will not serve as chairman of a session.

The following document addresses the specific issues raised and the corrective actions undertaken and proposed.

I again express my appreciation for the thorough examination of the BRI-IRB. Your examination has provided me with clear insight as to how we may improve our policies and alter our SOPs to align our operations in accord with the CFR.

Sincerely,

Carlton F. Hazlewood, Ph.D.
Chairman of the BRI-IRB

Detailed Responses

And

Corrective Actions

Observation 1

The IRB approved research without determining that the following criteria were met: that risks to subjects were minimized [21 CFR 56.111(a)(1)] and 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 [21CFR 56.111(a)(2)]

a. Evaluation of (b) (4) *for the* (b) (4) (b) (4)

You note that after the initial critical inspection of the (b) (4) application (b) (4) 1/10/2007) no discussion of this application ocurred until Feb. (2/1/2008) of the following year.

Response: Sponsors/Investigators did not reply to notification of the shortcomings of their application during this interval.

You note that at this time (2/1/2008) the committee was aware of [redacted] anecdotal case reports conducted at some unknown location at some earlier time. This is true. Indeed, the initial inspection of the (b) (4) application (b) (4) 1/10/2007) indicated that sponsor should provide provenance of these anecdotal reports. You assert that (b) (4) was treating patients with the drug at this time.

Response:Contrary to the apparent conclusion of the FDA inspection incorporated in the warning letter, the BRI IRB never gav(b)(4) approval to proceed with the clinical trials. That simply did not happen. The Sponsor/Investigator's application to the BRI/IRB posed many problems which would have to be addressed before the IRB would be able to assume responsibility for monitoring any proposed protocol. We were aware that animal toxicity studies were underway and we were also aware of the fact that the FDA had not released the sponsor's IND from clinical hold . Since our IRB was not involved in (b) (4) treatment of patients in his private practice, we did not feel we had the authority or jurisdiction to provide him with oversight and advice with regard to these patients.

You assert that subsequent to this meeting (by letter 2/15/2008) the IRB authorized (b) (4) to proceed with enrollment of human subjects.

Response: This letter to the investigator addressed the animal toxicity studies and not the approval of any human protocols. In support we point out that:

You note that on Aug. 8, 2008 the IRB again notified (b) (4) by letter that the IRB could not proceed with the application process until (b) (4) had obtained an approved IND from the FDA. A similar letter was sent to (b) (4) on Nov (11/02/2008) reiterating that their application was in abeyance awaiting toxicity studies and IND approval. You note that we did not cc investigator and sponsor for both these letters.

Response: The IRB did not keep good records with regard to inquires or requests that our IRB participate in possible or potential studies We now recognize that giving a potential study the same standard protocol number which we give our actual

studies introduces the possibility of misinterpretation. This issue will be addressed in the corrective action section to follow.

(b) (4)

You cite four letters from the IRB to the sponsor-investigator (1/06/2005, 3/17/2005, 3/23/2005, and 4/04/2005) asking for specific documents and modifications to elements of this application. In particular, you note the last letter indicated that the IRB could approve this protocol provided certain changes to the Investigator Brochure were made. You cite the IRB's inability to produce this document during the audit as an indication that the IRB had approved the protocol without that document hence the IRB could not judge cost/benefit.

Response: The sponsor-investigator was never able to obtain an IND from FDA and abandoned the contemplated research. The IRB points out that the study was never finally approved and did not accrue patients under the proposed clinical study. Until this was pointed out to us, our IRB did not treat the historical documentation of potential studies with the same care it applied to approved protocols under its purview. This issue will be addressed in the corrective action section to follow.

Corrective Actions – Observation 1

1) Establish practice of stamping all application communications with a disclaimer, e.g. "This communication is not to be construed as granting IRB approval or denoting IRB acceptance of responsibility for..... No patients may be enrolled until an IND is in affect and formal written IRB approval is granted"

2) Establish practice of assigning identification names and codes which distinguish applications and formal protocols.

3) Establish practice of ensuring communication with both the Sponsor and the Investigator.

4) In meeting agendas clearly separate formal protocol business from applications.

5) Incorporate the above in the IRB's SOPs.

Observation 2

The IRB failed to prepare, maintain, and follow written procedures for conducting its initial and continuing review of research [21 CFR 56.108(a) and 56.115(a)(6). Specifically, the IRB has no written procedure for conducting reviews of device studies to determine whether they involve a significant risk device and had no evidence that it had in fact conducted such reviews [21CFR 812.66].

You cite IRB approval of Protocol [redacted] Study") on July 21,2005 and its name change on August 10,2005. You note that the IRB did not document its review of the [redacted] device, or the NSR status of the device adequately. You also note that the IRB has no SOP for the evaluation of non-significant risk devices.

Response: In regard to the first specification, it is correct that the title of this study was changed. The title of the original proposal was shortened to [redacted] because of an understanding that the conditions listed originally could not be unified in one study. This did occur as a result of verbal conversations between members of the IRB and the PI. The shortened title seemed more appropriate in that it was limited to one disorder. We acknowledge that the change occurred without proper documentation, and steps are being taken to correct this limitation.

In regard to the second specification, the IRB did deliberate on the safety of the [redacted] device, and required that a professional engineer examine the [redacted] device in question. The device was found to be safe, and the report of the Professional Engineer was included in our first response to your warning letter. We acknowledged then, and we acknowledge now, that we did not fully document the examination. From our perspective, at the time of the audit, we considered that we had sufficient evidence that the device did not pose a significant risk. The professional engineer's findings on the specific device proposed for use in this study, along with the myriad of [redacted] devices used on human studies throughout the world (reviewed in the original protocol application) was taken as evidence that devices which interact with patients only through [redacted] pose no significant risk (absen[redacted] an[redacted] – which were addressed in study protocol).

Corrective Actions - Observation 2

1) The IRB will develop specific guidelines for documenting communication between the IRB and applicants. All phone discussions with applicant or Investigators to be documented in a telephone log.

2) Any substantive issues discussed by phone or E-Mail will be confirmed by letter from the IRB to the sponsor/investigator.

3) The IRB will develop specific procedures in our SOPs for the IRB (as well as the PIs and the Sponsors) in evaluating a device/drug for safety. A subcommittee of the current IRB will be formed for this specific purpose. The subcommittee will generate a written report to be presented to the complete board for final approval.

4) The IRB will also codify in its SOPs information that must be documented in its minutes and in the application forms available for the Principle Investigators and Sponsors.

Observation 3

The IRB failed to ensure that informed consent would be sought from each prospective subject or the subject's legally authorized representative in accordance with and to the extent to required by 21 CFR Part 50 [21CRF 56.111(a)(4)] and that informed consent would be appropriately documented in accordance with and to the extent required by 21 CFR 50.27 56.111(a)(5)]

a. For the (b) (4) *study, your inspection revealed no discussion about the informed consent document.*

You note that in meetings and communications with respect to this application between Feb1, 2008 and Nov. 3, 2008 there was no informed consent discussion and no informed consent document.

Response: There was no discussion of the informed consent document, because the application was on hold waiting for the toxicity study to be completed and IND obtained. Until (b) (4) **completed the animal toxicity studies the IRB did not and would not proceed with further consideration of the application. The BRI-IRB did not approve the clinical investigation. Please note that in our first response letter, under the discussion of** (b) (4) **the letter to** (b) (4) **of February 15, 2008 is clearly referenced to "Toxicity studies** (b) (4) **and the text further refers to these animal toxicity studies. Thus, every use of the word "study" was intended to address the animal toxicity study (see Exhibit 1 of our first response letter and appended here as Exhibit 1-A). In addition, the August 18, 2008 letter is addressed to** (b) (4) (b) (4) **(the sponsor) and carbon copied to** (b) (4) **(Principle Investigator). As you pointed out in your warning letter, the IRB clearly stated that the human study cannot be conducted without an approved IND. Furthermore, the letter begins in reference to:** (b) (4) **animal toxicity".**

b. For the (b) (4) *Study, the informed consent does not contain all the elements required by 21 CFR 50.25.*

i) You note the lack of a description of procedures, assessment forms, lab work and clinical testing required by the protocol.
ii) You note lack of accurate description of direct benefits
iii) You note lack of statement indicating possibility of FDA review of records
iv) You note lack of contact information for patient rights and in case of injury and incorrect identification of clinical investigator
v) You note lack of patient discontinuance without prejudice

Response: i) We accept that the informed consent document should be improved and, since the protocol is on hold, we shall request that a new consent form be generated that contains all the elements required by 21 CFR 50.25.

Response: ii) It was intended that the subjects to be included in this study should be informed of the anecdotal accounts of improvement should be included and that we were to conduct a study that would clearly elucidate the benefits (or lack there of). The protocol includes a discussion of the history of the field pointing out the need for a careful study.

Response: iii). Criticsm Accepted

Response: iv) Criticism Accepted

Response: v) Criticism Accepted

Corrective Action – Observation 3

1) All of the deficiencies noted in FDA Form 483, and additional deficiencies will be brought into compliance. A description of the study procedures, the lab work and all the clinical, neurological, and functional testing that will be required will be included in the consent form.

2) It will be required for the Sponsor and the Principle investigator to inform the subjects that The Food and Drug Administration may inspect the records according to 21 CFR 50.25(a)(5)

3) The consent form shall include an explanation of whom to contact for answers to pertinent questions about the research, the subjects rights, and whom to contact in the event of a research-related injury to the subject will be included in the consent form according to 21 CFR 50.25(a)(7). Also, (b) (4) will be correctly identified as the clinical investigator.

4) A statement that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is entitled.

Observation 4,

The IRB failed to insure that no member participated in the initial or continuing review of a project in which the member had a conflicting interest, except to provide information requested by the IRB [21 CFR 56.107(e)].

a. You note for the (b) (4) tudy, you (IRB Chairman, Carlton F. Hazlewood, Ph.D.) is listed as a clinical investigator on the "Certification: Financial Interests and Arrangements of Clinical Investigators"...Therefore you had a conflict of interest.

Response: It is correct that I led the meeting as chairman, I answered questions when asked, but I did not vote. Further, I was paid no money b (b) (4), and have no stock in the company—therefore; I had a no pecuniary potential conflict of interest. Nevertheless I did not vote on any issue relating to this application.

b. You note that for the (b) (4) Study, Roscoe L. Van Zandt, M.D. ([a] Vice Chairman of the IRB is listed on the protocol as a co-investigator. Minutes of the March 17, 2005 IRB meeting did not indicate that Van Zandt did not participate in the review which resulted in a letter to the sponsors requiring changes in their protocol and consent documents.

Response: There is a discrepancy between the number of voting members in particular sessions and registered number of votes. In the future, the minutes will clearly note who did vote and who did not. In the particular cases that are referred to in the Warning Letter it is likely an ambiguity in the minutes Care in the future will have to be taken to clarify "unanimous" (i.e., is it all voting members in the room, or voting members minus the chairman or someone leaving the room, or accidental inclusion of an invited guest). In the future, anyone with a known or potential conflict of interest will not serve as chairman of a session. Our practice and procedure is for the member with a potential or real conflict of interest to vacate the room until the voting is complete. After all discussion and the voting are completed, the administrator or another member leaves the room and asks such members to return. Because this is our standard procedure, the minutes did not reflect who left the room and who voted and did not vote. In the future we will make this more clear.

As a point of clarification, (b) (4) had been asked to attend this particular meeting of the IRB so he could be available when Dr. Van Zandt was absent.

Corrective Action – Observation 4

1) Our SOPs will be updated to formalize the conduct the meetings to eliminate as much of the ambiguity as possible – as follows

2) First, the chairman of the meeting shall not be an investigator on the study. The members present that can vote will be defined before the vote.

3) Our meeting agenda will clearly identify IRB protocols which are ongoing as distinguished from applications which are being developed. Those studies will be further characterized/labeled as "FDA IND – Request pending", "FDA IND – Request submitted", "FDA IND – Request denied or in discussion", and "FDA IND – Approved." Such labeling will remind and reinforce to our Board members that our role is minimal and limited to evaluating their IRB application until "FDA IND - Approved" status is achieved.

4) All correspondence with applicants will clearly identify our comments as limited strictly to elements of their application, as no human study can or should be initiated without IND approval and final IRB approval. Fourth, if the chairman has a potential/real conflict, the vice chairman will preside at the entire meeting.

Observation 5

The IRB failed to conduct continuing reviews for the following IRB approved studies [21 CFR 56.109(f)]:

(b) (4)

You note that in a series of letters the IRB approved the (b) (4) study contingent upon a series of changes in protocol and consent documents and subsequently informed the sponsor-investigator that these changes had been approved.

Response: Originally we were asked to review this protocol as a part of (b) (4) request for an IND to see if it could be "approved" (b) (4) thought that such a potential approval would help them obtain an IND. We approved his protocol contingent upon his obtaining the IND. We were confident that he would not proceed without the IND; and we were aware that he was in discussions with the FDA on this very matter. (Unfortunately, there were discussions by phone; and, at the time, we did not keep a running phone log.) It was well understood that that there could be no subject enrollment until they received an IND.

(b) (4)

You note that although no patients had been accrued to this study continuing review was obligatory. Your further note that verbal reports are not adequate means of conducting continuing reviews.

Response: We will correct this and continue to follow-up on inactive applications...

Corrective Action – Observation 5

1. SOPs will be updated providing explicit procedures for communicating with the Sponsor and/or the principle investigator.

2. Oral communication will be discouraged, and members of the IRB will be expected to reduce all communications to writing.

3. A telephone logging system will be developed to supplement the written communication, so that a clear record of documentation will be in our files.

4. No "contingent" approvals will be granted by the IRB under any circumstances.

Observation 6

The IRB failed to maintain copies of all research proposals reviewed, scientific evaluations, if any that accompany the proposals, approved sample consent documents, progress reports submitted by investigators and reports of injuries to subjects, and correspondence with investigators [21 CFR 56.115(a)(1) and 56115(a)(4).

a. The absence of the (b) (4) *Investigators Brochure*

You note the absence of the Investigators Brochure in our files during the original FDA audit

Response: This item was provided in our first response letter.

b. For the (b) (4) *study, an April 4, 2005 IRB letter to the sponsor-investigator refers to a copy of the protocol (including consent form). A copy of these documents was not maintained by the IRB.*

Response: These items were submitted with our first response letter.

c. For the (b) (4) *Study...*

You note (i) that although a letter from the engineer evaluating the (b) (4) apparatus was on file no letter requesting this evaluation was on file.

Response: It is correct that we did not write a letter to the professional engineer requesting the safety evaluation of the (b) (4) **, and we are unsure whether such a request must be in writing. Please advise. I contacted the sponsor and told him that the IRB wanted a professional engineer to evaluate the** (b) (4) **for overall safety—both electrical and mechanical. The letter, reporting the findings of the professional engineer was included in our first response letter.**

You note (ii) the change in the title of the (b) (4) protocol.

Response: As indicated previously the protocol title was shortened because of an understanding that the conditions listed originally could not be unified in one study. We acknowledge that we did document this procedure properly which we will rectify. Note: there was not another version of the protocol.

You note (iii) that although a "Tri-Fold Brochure" had been rejected by the committee the IRB failed to keep a copy of the brochure and the disapproval letter.

Response: A tri-fold was disapproved, and we understand that we did not document this matter properly.

Corrective Actions – Observation 6

1. A completely new filing system is being developed. A part-time person has been hired to help current personnel with this matter. Instituting this change has already improved our system.

2. SOPs will be updated to have clear language to outline procedures for documenting such matters as obtaining a professional engineer to conduct a needed evaluation for the IRB.

3. SOPs will be updated with explicit procedures for communicating with the Sponsor and/or the principle investigator.

3. Oral communication will be documented, and members of the IRB will be expected to reduce all communications with sponsors, investigators, potential sponsors, and between board members to writing.

4. As in observation 5, a telephone logging system will be helpful in supplementing the written communication, so that a clear record of documentation will be in our files

Observation 7

The IRB failed to prepare and maintain the minutes of the IRB meetings in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for , against, and abstaining ; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution [21 CFR 56.115(a)(2)].

a. It appears that the IRB tape records its meetings, which are then transcribed into a hard copy...

You note that during transcription from recorded tapes the minutes frequently contain gaps or poorly transcribed words making it occasionally difficult to identify the studies under discussion.

Response: You are correct. We have not regularly summarized these minutes into a more readable form.

b. For the (b) (4) study that was discussed at the February1, 2008 IRB meeting...

You note that although no action was recorded during this meeting a letter was sent 2 weeks later

Response: This error on our part seems to be a direct result of our past minute taking procedures. In regard to the IRB February 15, 2008 letter to (b) (4) approved only that the toxicity study continue. Unfortunately we had been using a general statement about "...adverse events and deaths to the sponsor and BRI-IRB". This will not be done in the future.

Corrective Action – Observation 7

1. Significantly modify taking and reporting of meeting minutes. The tape recording of the entire meeting will continue; however, scribes will be present to summarize important moments in the meeting. The meeting may be briefly paused in order to take contemporary notes—particularly during voting to insure accuracy of vote counting by qualified voters. A summary of all actions by protocol or application will be appended to the minutes.

2. Copies of all written communications with respect to protocols or applications shall be presented to the committee at the meeting following the authorization of such communications.

3. The IRB's SOPs will be re-written to incorporate these changes in the IRB's practices.

Observation 8

Each IRB is required to have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution [2] CFR 56.107(a)

You note that when a BRI IRB member has been absent or conflicted, a substitute non IRB member has been allowed to participate in IRB meetings. You cite several instances in which the vote totals on board actions and the number of board members present suggest that non-board members have been allowed to vote.

Response: On occasion a member will notify the IRB that they will be unable to attend a meeting. On this or a similar occasion the IRB may believe it needs a certain expertise, (in particular medical, ethical, or legal). In such instances the IRB will invite relevant parties to provide the lacking perspective or expertise. However in no case are non-members ever allowed to vote on IRB actions. Any discrepancies between vote count and IRB members present is the result of incorrect recording of unanimous votes.

Corrective Action – Observation 8

1. Significantly enhance the reporting of meeting votes. A sign-in sheet will continue to be used however when guests are present, every vote will be recorded in a tally format.

2. The IRB's SOPs will be re-written to incorporate these changes in the IRB's practices.