

Independent Review Consulting, Inc.

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August 6, 2010

Via FAX and Federal Express

Anne T. Hawthorne
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance
Division of Research Monitoring
10903 New Hampshire Avenue
Building 66, Room 3504
Silver Spring, MD 20993-0002

Re: July 19, 2010 Warning Letter
Reference: CTS# EC100202/E001

Dear Ms. Hawthorne,

This letter is our response to the FDA's July 19, 2010 Warning Letter.

We appreciate the seriousness of the issues raised and are carefully addressing them both specifically and systemically.

Our response to each of the four specific items listed in your Warning Letter are presented on the following pages. In each case we have included written documentation of the additional actions we have taken, or will take, to correct the conditions noted and to prevent the recurrence of similar conditions in the future.

We welcome the opportunity to meet with you in order to discuss the issues addressed in the Warning Letter along with our response in order to assure that our actions are in complete alignment with FDA's regulations. Should you believe that it would be of assistance, please advise us to arrange a schedule. We will contact you to inquire about the advisability next week.

If you have any questions regarding this response or need additional information, please feel free to contact me

Sincerely yours,

Signed copy by mail

Erica Heath, CIP, MBA, President IRC

IRC





ITEM 1

1. Failure to use expedited review procedures only for certain kinds of research involving no more than minimal risk or for minor changes in approved research [21 CFR 56.110, 21 CFR 56.108(c)].

The IRB granted approval by expedited review of research for a significant risk study that did not meet the criteria provided for in 21 CFR 56.110. Examples of your failure include, but are not limited to the following:

- The [REDACTED] (study A) Study was approved via expedited review rather than at a full board meeting. The [REDACTED] Study is a significant risk study, involving more than minimal risk, and is not within the categories of research on the list at 63 FR 60353 (November 9, 1998). The study is, therefore, not eligible for expedited review."

Your written response states that the understanding of the board was that the device was not investigational and therefore, qualified for expedited review. Your response also states that the IRC Administration has determined that a more precise declaration of device status may aid in the prevention of future confusion, and increase the assurance of regulatory compliance and subject safety. In order to achieve this goal, you explain, revisions have been made to the Device Supplement Application Form 4.13B and training of staff and board members would occur no later than April 1, 2010.

Your response is incomplete in that it does not describe how you will verify whether the study involves no more than minimal risk. Please submit your revised procedures pertinent to Form 4.13B, including procedures on how you will determine whether a study involves no more than minimal risk. Please also provide information regarding the dates when your staff and members of the board were trained on this revised procedure.

Response:

The IRB will verify that the study involves no more than minimal risk through use of two documents. First, the applicant must submit a form titled "Supplement A: Justification for Request for Expedited Review, Form 4.13A". (Attachment 1A) Page 1 of this form asks the applicant to suggest an appropriate category and risk level. The full definition of minimal risk as defined in 21 CFR 56.102 is included on page 1 to assist the applicant in their response. This form is provided to the IRB member / reviewer, who verifies the category claimed by the applicant and documents that verification on the "Reviewer Checklist, Expedited Review Study" form. (Attachment 1C) As a result of FDA's observation listed above, we have revised this form (also attached) to more clearly note the reviewer's determination if, in his or her assessment, the risk level is no more than minimal risk, and identify the category by which this determination is made. We have also included a series of specifically designated check boxes in the revised form for specific determinations.

Our revised procedures pertinent to Form 4.13B (Attachment 1B) are as follows:

1. Form 4.13B is only used for determination of regulatory status of a device.
2. A device that is investigational and is not exempt under 21 CFR 812.2(c) ("This part,

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with the exception of Sec. 812.119, does not apply to investigations of the following categories of devices") must be reviewed by full board.

3. If the device is exempt or not investigational it is eligible to be considered for expedited review.
4. If the device is reviewed under expedited review procedures, determination of no-more-than-minimal-risk will be made using Form 4.13A.

Our procedures regarding the use of Form 4.13A (Attachment 1A) to determine no more than minimal risk are as follows:

1. The expedited review application form (4.13A) contains the entire definition of minimal risk provided in 63 FR 60353.
2. The full application, including the supplemental form is logged into a database.
3. The reviewer receives the entire application including the investigator's initial evaluation and the expedited initial review checklist generated from the database.
4. Question 1 on the checklist asks the reviewer to determine whether the study presents no more than minimal risk of harm. The full definition is provided on the application for the reviewer's reference.
5. Should the reviewer agree with the applicant's determination that the study presents no more than minimal risk of harm, along with answers provided to other questions, the checklist is completed and signed. Should the reviewer disagree, the study is either returned for further information or is referred to the full board for review.
6. Finally, the reviewer's decision is provided to the board in Report 1 which is attached to a board meeting agenda. Board members then review the report and have an opportunity to ask the reviewer for further detail.

To further explain the relationship between these forms, the following table illustrates our decision tree process:

Device Status per 21 CFR 812.2		No more than minimal risk determination per 21 CFR 56.102	Expedited Review?
The device is not FDA regulated? (Form 4.13B, Question A4a)	AND	Is the study no more than minimal risk? (Form 4.13A)	Possible, if all procedures fit categories
Is the device exempt from IDE under 812.2c? (Form 4.13B, Question A4b,iii)	AND	Is the study no more than minimal risk? (Form 4.13A)	Possible, if all procedures fit categories
Does the device have an IDE? (Form 4.13B, Question A4b,i)			Not allowed.
Is the device NSR? (Form 4.13B, Question A4b,ii)			Not allowed.

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These procedures are found in the IRB Standard Operating Procedures (Attachment 1F) and in staff process instructions (called Elaborations) (Attachment 1D AND 1E).

Our staff was most recently re-trained on the determination of minimal risk on August 3, 2010. Attached is documentation of the staff training session. (Attachment 1G)

The members of our board received their most recent re-training at the regular meeting of August 3, 2010. Attached is a copy of the draft minutes of that meeting. (Attachment 1H)

Under IRC's expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB. In the study cited above, the reviewer was the IRB chair who has been an IRB member since 1998 and has attended internal training sessions and national training sessions at the Public Responsibility in Medicine and Research (PRIM&R) annual conference on topics such as research ethics, human subject protection and good clinical practices.

- Attachments:**
- 1A** Form 4.13A, Supplement A: Justification for Request for Expedited Review,
 - 1B** Form 4.13B, Supplement, Devices
 - 1C** Reviewer Checklist, Expedited Review Study - Revised
 - 1D** Elaborations and Instructions, 302.01 Expedited Review Process
 - 1E** Elaborations and Instructions, 302.05 Expedited Review Categories
 - 1F** Portion of IRB Standard Operating Procedures, April 2009: Section III.4.B.
 - 1G** Staff training (August 3, 2010) signature page (One staff member is on vacation and will be trained upon his return.)
 - 1H** Draft Copy of August 3, 2010, Minutes – page 1- Including Training



ITEM 2

2. Failure to prepare and maintain adequate documentation of IRB activities, including minutes of IRB meetings, which shall be 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)].

Minutes of the IRB meetings are inaccurate and/or incomplete. Examples of this failure include, but are not limited to the following."

- *The meeting minutes for both the February 10, 2009, and February 24, 2009 meetings regarding the [REDACTED] (STUDY B) Study should have included discussion regarding the controverted issues that ultimately prompted letters being sent to the principal investigators.*

Your written response states that the existing format for meeting minutes failed to communicate as effectively as you prefer, therefore, the format for meeting minutes will be amended to include more descriptive language and explanation, and board members and staff would be trained no later than April 1, 2010.

Your response is inadequate in that it does not describe the details of your plan to change the minutes format or whether you plan to revise your written procedure for preparing minutes. Please provide FDA with this information including a copy of the amended format for meeting minutes, and, if applicable, a copy of your revised written procedure for preparing minutes. Please also include information regarding the dates board members and staff were trained on the revised meeting minutes format and, if applicable, revised written procedures for preparing minutes

Response:

We have changed the minutes format to require detailed documentation of the discussion. The revised minutes template specifically requires documentation of (a) controverted issues, regardless of resolution, (b) issues discussed and resolved, (c) issues discussed but not resolved that need resolution prior to approval, and (d) other discussion, as applicable. This format provides a summary of discussion and actions including the basis for requiring changes in, or disapproval of, the research; and a written summary of the discussion of controverted issues and their resolution. For controverted and / or unresolved issues that require follow-up, our procedures require a letter be sent to the principal investigator(s) requesting clarification or modification.

Attached is a copy of our amended format for meeting minutes (Attachment 2A) with sample documentation of discussion. Please note the discussion section for initial and continuing review. The first of the four headers are for controverted issues, described as any that involve controversy or substantive debate among members. Our procedure to either note "None" or to include discussion that was controverted; that is, with controversy. Those discussion items without controversy are documented in the three other headers.

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IRC has to Elaborations directed to staff regarding their duties during the full board meeting (Attachment 2B) and the writing of minutes (Attachment 2C)

Attached is documentation of the staff training session (August 4, 2010) at which the four discussion categories were reviewed. (Attachment 2D)

The members of our board are not responsible for writing the minutes; however, they were trained on reviewing them for content. (Attachment 2E) They will receive their training at the regular meeting of August 10, 2010. Attached is a copy of the training materials for that meeting. (Attachment 2D)

Note:

In neither of the research studies cited by FDA in the Warning Letter were there discussion of any “controverted” issues. The reason is that there were no controverted issues. Thus, there was no discussion of controverted issues reported on the minutes. There were several issues about which there was some discussion where the board was in agreement that further information was required; however, there was no controversy or discussion of alternative viewpoints. Nevertheless, the procedure and meeting minutes format have been changed to improve documentation of discussions when no controverted issues are raised.

- Attachments:**
- 2A** Current Minutes Template
 - 2B** Elaboration 305: Staff Duties During Meeting
 - 2C** Elaboration 307: Minutes
 - 2D** Staff Training Agenda and Signature Page
 - 2E** IRB SOP Section VII C.1. Minutes



ITEM 3

3. The IRB failed to ensure the information given to subjects as part of informed consent is in accordance with 21 CFR 5025 [21 CFR 56.109(b)] This is a reoccurrence of a violation cited in the last IRB inspection and the last Untitled Letter issued to you in 2008.

The IRB shall require that information given to subjects as part of informed consent is provided in accordance with 21 CFR 50.25 (21 CFR 56.109(b)). The IRB failed to ensure that informed consent contained all the information required by 21 CFR 50.25 such as:

- [REDACTED] **(Study A)** Study: the informed consent document utilized for this study did not contain a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained and that notes the possibility that the Food and Drug Administration may inspect the records (21 CFR (sic) 50.25(a)(5)).
- [REDACTED] **(Study C)**: the informed consent document utilized for this check did not contain an explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights and whom to contact in the event of a research-related injury to the subject (21 CFR 50.25(a)(7)).

Your written response states that in order to ensure improved oversight, you are revising your process to include more support of the board members' review through more staff involvement of screening the submission documents. In addition, your response states that training on these procedures was conducted on March 2, 2010.

Your response is inadequate in that it did not describe how you will revise your processes to ensure subjects are provided informed consent in accordance with 21 CFR 50.25. Please also clarify how staff involvement in screening will ensure subjects are provided informed consent that is in accordance with 21 CFR 50.25, e.g., an explanation of whom to contact for answers to pertinent questions about the research, the research subjects' rights, and whom to contact in the event of a research-related injury to the subject.

Response:

The checklist has been modified to specifically address confidentiality of records and the possibility of FDA inspection of the records. Instead of one single check box for multiple confidentiality provisions, the checklist now includes specific check boxes to verify that (a) confidentiality provisions are included in the consent form, (b) notification of Sponsor access to the records is included in the consent form, where appropriate, (c) notification of IRB access to the records is included in the consent form, where appropriate, and (d) notification of the possibility of FDA inspection of the records are included in the consent form. This meets the requirements in 21 CFR 50.25(a)(5).

The checklist has also been modified to specifically address contact information requirements. The checklist now contains specific check boxes to verify that contact information is provided for (a) study information and study subject's rights, (b) IRB contact for concerns and complaints regarding the study, (c) harm / injury during or resulting from

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the study, and (d) (for California) sponsor contact for long term effects resulting from the study. This meets the requirements in 21 CFR 50.25(a)(7).

Attached are copies of the revised Checklist and Instructions for using the checklist. These instructions are provided to all staff, the Board, and individual reviewers (in the case of expedited review).

As an additional measure to assure that each required item is addressed in consent forms, we have revised our procedures to include staff review of the consent document and checklist prior to IRB review. Staff review is not intended as a substitute for Board review; however, staff will check for compliance; and Board members continue to review for compliance and content. This additional process will serve as a "double-check" to assure that the required elements are included in the consent form. Should the consent form be altered during review, the same checklist will be used by both the Board and staff person to insure that the consent form is in compliance.

Additional training on these elements of informed consent was provided to staff on July 27, 2010; and to members of the Board on July 27, 2010. In addition, IRC will provide training to each new staff person or Board member, and include training updates once a year.

Notes:

The informed consent document utilized for the [REDACTED] (Study A) Study did include a statement describing how confidentiality of records identifying the subject was to be maintained: "Unless required by law, only the investigator ([REDACTED]) will have access to your medical information or other confidential information or information of a personal nature. The sponsor of this study ([REDACTED]) will have access to the results of these case clinical studies. However, these results will be delinked, i.e. your personal information will be removed prior to sending these results the sponsor. You will not be identified by name in any reports or publications resulting from this evaluation, although photographs of your lower limbs may be used in scientific and educational literature."

The informed consent document utilized for the [REDACTED] (Study C) study contained the following contact information: "If you have questions about this study, its procedures, risks or benefits, please contact [REDACTED] at [REDACTED]. She is the person in charge of this research study. If you have complaints or questions that you don't believe that you can discuss with the investigator, you may call Independent Review Consulting, an independent, impartial reviewer. You may reach them at PO Box 170, San Anselmo, CA 94979 or at (800)-472-3241. IRC's e-mail contact for subjects is subject@irb-irc.com"

- Attachments:**
- 3A** Revised IRC Consent Form Checklist, No. 330.03
 - 3B** Elaborations and Instructions, 330.01
 - 3C** Draft Copy of July 27, 2010, Minutes Including Training
 - 3D** Staff training (July 27, 2010) signature page (One staff member is on vacation and will be trained upon his return.)



ITEM 4

4. In approving research covered by the regulations, the IRB failed to determine that risks to subjects are minimized, 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. [21 CFR 56.111(a)(1), (a)(2)]

In order to approve research, the IRB reviewed the protocol entitled "[REDACTED], (Study D)" version 12/07/09 submitted by the study sponsor [REDACTED] Inc. However, during its review, the IRB did not determine that risks to subjects are minimized or reasonable in relation to anticipated benefit, if any, to subjects and the importance of the knowledge that may be expected to result. For example, the IRB did not review or determine that risks to subjects are minimized, 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 regarding the risk of loosening of teeth or wear on dental enamel after long term exposure to the device or the risk of swallowing the dental appliance.

Response:

The study cited in FDA's warning letter was the third in a series of four related studies dating from November, 2007. The previous two related studies were:

07014 [REDACTED]

08132 [REDACTED]

Each of these studies had been reviewed by the full board at a convened meeting. During the course of those previous reviews, several letters raising a number of concerns were sent to the Sponsor requesting clarification or modifications to those protocols. In addition to the risk of swallowing, the board had discussed other study risks including those stemming from therapeutic misconception, possible cuts from sharp corners or projections, the risk of seizures, care instructions, and problems with eating. These concerns were resolved on the previous studies to the Board's satisfaction.

During review of the "[REDACTED]" study cited in the Warning Letter:

- The IRB met in convened meeting on December 1, 2009 to review study version 11/20/09. The board members discussed the similarities and differences between this study and the previous studies, discussed the risks mentioned and were satisfied with the description and risk evaluation for use of the device for the duration of wear requested. The device submission form (form 4.13B) identified the risks from the [REDACTED], the potential for swallowing and the potential for [REDACTED]. The board issued a letter dated 12/02/09 in which nine questions or requirements were raised.
- The IRB met in convened meeting on December 15, 2009 to review study version 12/07/09 which was found to be responsive to the points raised.

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The meeting minutes for the meetings at which this protocol was reviewed; although referencing the prior study, did not adequately document the discussion regarding the similarities and differences among this study and the previous studies; and the discussion regarding risks and benefits. We have changed the minutes format; therefore, to require detailed documentation of the discussion. Please refer to our response to Item #2 above.

Attachments: A side-by-side comparison of the questions raised in prior studies and discussions from the minutes.

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APPENDIX

Attachments: Copy of FDA's 483 Form
Copy of IRC's Response (date)
Copy of FDA's Warning Letter