



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville, Maryland 20850

MAR 27 2006

WARNING LETTER

VIA FEDERAL EXPRESS

John Brown, M.D.
Riley's Children's Hospital
702 Barnhill Drive, Room 104
Indianapolis, Indiana 46202-5125

Dear Dr. Brown:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site from [REDACTED] by an investigator from FDA's Detroit District Office. The purpose of the inspection was to determine whether activities and procedures related to your participation in the clinical study of the [REDACTED] [REDACTED] complied with applicable federal regulations. The [REDACTED] is a device, as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h). This letter also requests prompt corrective action to address the violations cited and discusses your written response to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and Premarket Notification submissions (510(k)) are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 C.F.R.), Part 812 - Investigational Device Exemptions and Part 50- Protection of Human Subjects.. At the close of the inspection, the FDA investigator presented an inspectional observations form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:



Protecting and Promoting Public Health

Legally effective informed consent was not obtained from a subject or the subject's legally authorized representative (21 CFR 812.100, 50.20, 50.23, and 50.27).

You failed to ensure that the current IRB-approved version of the informed consent was executed for each of the subjects enrolled in the studies as required by the above-stated regulations. Examples of this failure include but are not limited to the following:

You did not obtain written informed consent, prior to [REDACTED] in the following cases:

- Subject [REDACTED] on 11/20/03, but consent was not obtained from the parent. This patient died prior to discharge, and the death was not reported to the IRB or sponsor in a timely manner.
- Subject [REDACTED] as an emergency on 1/16/04, while the consent was obtained from the parent on 3/29/04.
- Subject [REDACTED] as an emergency on 5/4/99, while the consent was obtained from the parent on 6/2/99.
- You did not obtain the assent of 12 subjects who were children seven and older as required by the IRB-approved consent form.
- The IRB-approved consent form required the signature of a witness yet the informed consent forms for subjects [REDACTED] did not have the signature of the person who witnessed the signing of the consent form. The informed consent form for subject [REDACTED] was signed on 6/11/03 and witnessed on 7/10/03, and for subject [REDACTED] was signed by the subject's parent on 3/29/04 and witnessed on 1/4/04.

In addition, the form used to document informed consent for the following patients was expired: [REDACTED]

Your October 28, 2005 response to the form FDA 483 indicates that you notified the sponsor, FDA, and/or the IRB of your failure to obtain written informed consent before using the test article, from Subjects [REDACTED]. However, obtaining of informed consent prior to use of the test article is deemed feasible unless, before the use of the test article, both the investigator and a physician who is not otherwise participating in the clinical investigation certify all of the following which are listed in 21 CFR 50.23(a):

- The human subject is confronted by a life-threatening situation necessitating the use of the test article.

- Informed consent cannot be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from the subject.
- Time is not sufficient to obtain consent from the subject's legal representative.
- There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject.

██████████ co-investigator, provided the certification for the items listed above. As co-investigators in the study of this device, neither you nor ██████████ are "not otherwise participating in the clinical investigation" and therefore cannot provide this certification.

The investigation was not conducted according to the signed agreement, investigational plan, and applicable FDA regulations (21CFR 812.110(b), and you failed to submit required reports, 21 CFR 812.150(a)(4).

You failed to adhere to the above-stated regulations. Examples of this failure include but are not limited to the following:

- Two subjects in whom you ██████████ ██████████ using the guidelines for compassionate use of an unapproved medical device were deviations from the open IDE protocol for which you did not obtain the required approval. Prior to implementing protocol deviations for non-emergency cases, the study protocol requires approval in writing by the sponsor, and approval by the IRB. Subject ██████████ who did not meet study inclusion criteria (age 26), ██████████ on 11/30/01 without prior IRB and sponsor approval, and subject ██████████ who did not meet study inclusion criteria (age 37), ██████████ on 1/4/02 without prior approval from the sponsor.
- On 8/2/01 you ██████████ subject ██████████ with the ██████████ under the guidelines for emergency use of an unapproved medical device, but this was a deviation from the protocol, as the subject did not meet the IDE study inclusion criteria. You failed to notify the sponsor, as required by the protocol.
- On 5/4/99 you ██████████ subject ██████████ with the ██████████ under the emergency use of an unapproved medical device guideline, but you did not notify the IRB of this ██████████ as required by the protocol and 21 CFR 812.150(a)(4). Your October 28 response indicates that the sponsor and FDA were notified of these protocol deviations, but you did not obtain prior IRB approval.

Your response indicates that you have instituted corrections to your procedures for obtaining informed consent, to prevent future recurrences of these problems. This response is not adequate as it does not describe how the corrections will prevent recurrences. Please include any new procedures in your response.

In addition, during discussion with you at the close of the inspection, the FDA investigator noted that there were no device accountability records for the HDE devices and no evidence that you reviewed device accountability records.

Your October 28, 2005 response addresses each of the FDA 483 items and in a few instances it states that steps have been taken to correct these deviations, but in most cases, it does not specify what steps have been implemented or how they will prevent future deviations. In general, your response indicates a lack of understanding of the regulatory requirements that clinical investigators must meet and includes few corrective actions taken or planned, with regard to the deviations noted during the inspection. It is important for a clinical investigator to understand that unless the physical safety of a subject demands otherwise, treatment of study subjects must adhere to the requirements of the investigational plan. Please explain how you will ensure these deviations do not recur and include any new or amended procedures with your response.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a clinical investigator to ensure compliance with the Act and applicable regulations.

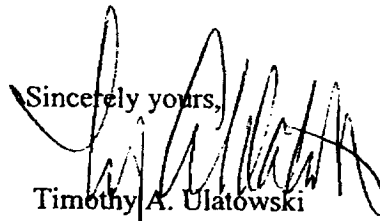
Within fifteen (15) working days of receiving this letter, please provide written documentation of the actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the clinical investigator. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you. In addition, FDA could initiate disqualification proceedings against you in accordance with 21CFR 812.119.

You will find information to assist you in understanding your responsibilities and planning your corrective actions in the FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at <http://www.fda.gov/oc/ohrt/irbs/>. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Send your response to: Attention: Viola Sellman, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, 2098 Gaither Road, HFZ-310, Rockville, Maryland 20850.

A copy of this letter has been sent to the Detroit District Office. Please send a copy of your response to: Joann Givens, Director, Detroit District Office, U.S. Food and Drug Administration, 300 River Place, Suite 5900, HFR-CE700, Detroit, MI 48207

Page 5 – John Brown, M.D.

If you have any questions, please contact Viola Sellman at (240) 276-0125 or viola.sellman@fda.hhs.gov.

Sincerely yours,


Timothy A. Ulatowski
Director
Office of Compliance
Center for Devices and
Radiological Health

cc:

[Redacted]