

Inspections, Compliance, Enforcement, and Criminal Investigations

Feins, Neil R., M.D.



Department of Health and Human Services

Public Health Service
Food and Drug
Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

WARNING LETTER

VIA FEDERAL EXPRESS

MAY 20 2009

Neil R. Feins, M.D.
Professor of Surgery
Children's Hospital Boston
300 Longwood Avenue, Fegan 3
Boston, Massachusetts 02115

Dear Dr. Feins:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at your clinical site during the period of February 4, 10 and 17, 2009 by an investigator from the FDA New England District Office. The purpose of this inspection was to determine whether your activities as a sponsor and a clinical investigator related to the clinical study entitled **(b)(4)** using the investigational device **(b)(4)** complied with applicable federal regulations. **(b)(4)** 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, dated February 23, 2009, 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 and **(b)(6)**. The deviations noted on the FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

Failure to adhere to informed consent requirements. [21 C.F.R. 50.20, 50.25, 50.27, and 50.55(f)]

The regulations prohibit an investigator from involving a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. 21 C.F.R. 50.20. Moreover, informed consent is required to be documented by the use of a written consent form approved by the Institutional Review Board (IRB), and signed and dated by the subject or the subject's legally authorized representative at the time of the consent. **(1)** 21 C.F.R. 50.27(a), and 50.55(f).

- There was no documentation that a parent signed and dated an informed consent form (ICF) for one subject **(b)(6)**.
- You did not use the **(b)(6)** approved ICF for the subjects enrolled in this study. As a result, the ICF you used failed to include information from the IRB approved form such as: cost to the subject, a privacy statement, or a financial

conflict of interest statement.

- In addition, it appears that someone other than the parent dated the consent forms for subjects **(b)(6)**

The ICF must include all the basic elements of informed consent enumerated in 21 C.F.R. 50.25.

- The ICF you used did not consistently include all the basic elements of informed consent. For example, the ICFs for six subjects **(b)(6)** did not include a statement that the Food and Drug Administration may inspect the records in its confidentiality provision.

The regulations require that the ICF include a description of any reasonably foreseeable risks or discomforts to the subject. 21 C.F.R. 50.25(a)(2).

- The ICF you used contained positive statements of the investigational device's safety and effectiveness that are misleading with respect to foreseeable risks of the device. For example, under the "Risks and Discomforts" section, the ICF states that **(b)(4)** is an FDA approved substance safely and successfully **(b)(4)** for over 10 years."

In your response, you acknowledge that you should have been using the **(b)(4)** approved ICF and agree that in the future you will use the proper consent form. Moreover, you state that you will make sure that the legally authorized representative both signs and dates the form at the time the informed consent is given. Your response is inadequate in that you failed to provide any new or revised policies and procedures that will ensure informed consent is obtained in accordance with the above stated regulations for future studies involving FDA regulated products. Submit a copy of these procedures in your response to this letter.

Failure to conduct an investigation according to the signed agreement, the investigational plan, and applicable FDA regulations [21 C.F.R. 812.100 and 812.110(b)]; failure to obtain approval prior to implementing a change to the investigational plan [21 C.F.R. 812.35].

An investigator is responsible for ensuring that an investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations. 21 C.F.R. 812.100, and 812.110(b).

- You failed to conduct the investigation in accordance with the investigational plan in that you enrolled subjects who did not meet the eligibility criteria set forth in the investigational plan. Examples of your failure include, but are not limited to the following: The inclusion criteria in the protocol specified that **(b)(4)** were eligible for study enrollment. However, you enrolled **(b)(6)** who were between **(b)(4)** and **(b)(4)** years old and treated them with the investigational device.

Because you are both a clinical investigator as well as the sponsor for this study, you are required to fulfill the responsibilities of each. As a sponsor, you are required to obtain FDA approval and IRB approval when appropriate, and prior to implementing a change to the investigational plan. 21 C.F.R. 812.35.

- You failed to obtain FDA approval for changes to the inclusion criteria.

In your response, you indicate that the age range in the protocol and the IDE was an error, as the intent of the study was to use a minimally invasive method of closure in the pediatric population that had failed to **(b)(4)** in the usual allotted time of **(b)(4)** and would need open **(b)(4)**. You indicated that in any future studies, the age discrepancy will be corrected. Your response is inadequate in that you did not obtain FDA approval for the changes in the inclusion criteria, nor did you submit any documentation reflecting the corrective or preventive actions you have implemented to ensure that this deviation does not recur. Please develop procedures that will prevent the above deviation from recurring in future studies. Submit a copy of these procedures, along with documentation demonstrating staff training in these procedures, when you respond to this letter.

Failure to maintain accurate, complete, and current records related to your participation in the investigation. [21 C.F.R. 812.140(a)]

A clinical investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation: records of receipt, use or disposition of a device that relate to the type and quantity of the device, the dates of its receipt, and the batch number or code mark. 21 C.F.R. 812.140(a)(2)(i).

- You failed to adhere to the above stated regulation. Examples of this failure include, but are not limited to the following: Your device receipt and disposition records were inadequately maintained. You reported that you received enough from not have any documentation of the exact quantity received. You provided a spreadsheet pertaining to device accountability at the close of the inspection; however, it did not state the quantity of device received nor did it provide the date of its receipt.

Your response states that the nurse in the designated **(b)(4)** kept a separate log relating to the quantity, date, and lot number of the device. This log was kept in the cabinet with the devices; however the log and the nurse were not available at the time of the FDA inspection. You stated that you subsequently provided the patient names, lot numbers, and amount given. Your response is inadequate. The spreadsheet you provided did not include the quantity of device received or the date on which they were received. Moreover, your response does not provide substantive corrective actions or any preventive actions to ensure appropriate device accountability and to avoid recurrence of these violations. Please provide us with documentation of a corrective action plan, such as written standard operating procedures (SOPs) and written verification of training received by you and your study staff on study procedures to ensure proper record keeping.

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 the study sponsor and 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 sponsor and 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.

You will find information to assist you in understanding your responsibilities 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: Linda D. Godfrey, Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, WO66 RM3462 G/H, 10903 New Hampshire, Silver Spring, Maryland

20993.

A copy of this letter has been sent to the New England District Office, One Montvale Avenue, 4th Floor, Stoneham, Massachusetts, 02180. Please send a copy of your response to that office. If you have any questions, please contact Ms. Linda Godfrey by telephone at (240) 276-0125 or via e-mail at Linda.Godfrey@fda.hhs.gov.

Sincerely yours,

/S/

Timothy A. Ulatowski

Director

Office of Compliance

Center for Devices and

Radiological Health

(1) An IRB may require information, in addition to that specifically mentioned in 21 CFR 50.25, to be given to subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects. 21 C.F.R. 56.109(b).