



g4435d

DEC 11 2003

WARNING LETTER
Via Federal ExpressFood and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Stephen H. Caldwell, M.D.
University of Virginia Health Systems
Division of Gastroenterology and Hepatology
2nd Floor West Complex
Jefferson Park Avenue
Charlottesville, Virginia 22908

Dear Dr. Caldwell:

The purpose of this Warning Letter is to inform you of significant violations of regulations concerning the obligations of study sponsors that were found during a Food and Drug Administration (FDA) inspection conducted at your clinical site and to request a prompt reply. The inspection took place during the period of August 19 through 21, 2003 and was conducted by Ms. Candice C. Manderla, an investigator from FDA's Baltimore District Office. The purpose of the inspection was to determine if your activities as a sponsor-investigator of a study entitled [REDACTED] comply with applicable FDA regulations. As a sponsor-investigator, you are responsible for complying with regulations pertinent to both a sponsor and a clinical investigator. Enbucrilate is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

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 [510(k)] submissions 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 submitted by the district office revealed serious violations of requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, and Part 50 - Protection of Human Subjects. You received a Form FDA 483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed with you. The violations revealed during this inspection concern your failure to fulfill the responsibilities of a study sponsor (21 CFR 812.40).

The inspection report notes that you stated you were unaware you were considered the study sponsor until July 2001 when you were informed by the institutional review

board (IRB) at the [REDACTED] had rescinded approval for the study at the [REDACTED] conducted by [REDACTED] as a result of their failure to report a serious adverse event. However, it should have been clear to you from the time you first received correspondence from FDA concerning your IDE submission that you were the study sponsor. The following communications clearly indicated that you were the study sponsor:

- On [REDACTED] the reviewing division of the Office of Device Evaluation (ODE) sent you a letter (copy enclosed) that was addressed "Dear Sponsor" to confirm receipt of your IDE and to assign you an IDE number.
- To clarify any confusion over who the sponsor of the study was, a member of the Gastrointestinal and Renal Devices Branch of ODE called the study coordinator, [REDACTED] and confirmed that you were the sponsor-investigator. A copy of the first page of the memo to the file that documents this conversion is enclosed.
- On [REDACTED] granted FDA permission (copy enclosed) to access the Device Master File for purposes of your IDE submission. If [REDACTED] had been the sponsor of the study, it would not have been necessary for them to grant FDA permission to access the master file.
- The IDE approval letter of [REDACTED] from the reviewing division in ODE (copy enclosed) states that a guidance document available at that time, entitled "Sponsor's Responsibilities for a Significant Risk Device Investigation," was enclosed to help you understand the functions and duties of a sponsor.
- Finally, an [REDACTED] letter (copy enclosed) from ODE addresses you as the sponsor of the study and requests your submission of the required IDE progress report which was then overdue.

Sponsors are responsible for selecting qualified investigators and providing them with the information they need to conduct the investigation properly, ensuring proper monitoring of the investigation, ensuring that IRB review and approval are obtained, submitting an IDE application to FDA, and ensuring that any reviewing IRB and FDA are promptly informed of significant new information about an investigation.

The inspection report notes that the study is presently active at only your site. However, inspectional findings revealed the following specific deviations with regard to your responsibilities as the study sponsor during the time the study was conducted at multiple sites:

**Failure to ensure that IRB approval was obtained at each investigational site
(21 CFR 812.42)**

No documentation was available at the time of the inspection to show that the study as conducted at the [REDACTED] had IRB review and approval. You were also unable to supply either the address of the University's

IRB or the name of its chair. A sponsor cannot initiate an investigation or any part of an investigation without IRB approval.

Failure to obtain signed investigator agreements from study investigators (21 CFR 812.43(c))

The inspection report notes that you did not obtain signed investigator agreements for either the [REDACTED] or the [REDACTED] site. A study sponsor is responsible for obtaining signed agreements from each of the investigators participating in the study.

Failure to properly monitor the study (21 CFR 812.25, 812.43(d), and 812.46)

Investigational findings revealed that you did not have written standard operating procedures for monitoring the study, did not choose qualified monitors to oversee the study, and did not ensure that participating investigators at either the [REDACTED] or [REDACTED] sites conducted the study according to the investigational plan and applicable FDA regulations.

Failure to maintain adequate device accountability records (21 CFR 812.140(b)(2))

Device logs inspected revealed you did not maintain adequate records of the shipment and disposition of the investigational device. Sponsors are required to maintain accurate, complete, and current records of the shipment and disposition of all investigational devices. These records are to include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. In addition, records of disposition need to include the batch number or code marks of any devices returned to the sponsor, repaired, or disposed of in other ways as well as the reasons for and methods of disposal. Your records were not adequate in several respects including that there were no records for shipment of certain lots and there was no documentation of the disposition of the devices at the [REDACTED] and [REDACTED] sites.

Moreover, logs reviewed during the inspection accounted for the use of the device for only 57 of 62 study subjects at your site. As a clinical investigator, 21 CFR 812.140(a)(2) requires you to maintain accurate, complete, and current records of the receipt and disposition of all investigational devices used at your site, including the names of all persons who received the device.

The deviations listed above are not intended to be an all-inclusive list of deficiencies that may exist in your clinical study. It is your responsibility as a sponsor-investigator to ensure that an investigation is conducted according to a signed agreement, the investigational plan, and applicable FDA regulations.

Please inform us, within 15 working days of receipt of this letter, of specific corrective actions you have taken or plan to take to ensure that the deviations noted

are not repeated in this study or future studies. Please send your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Jean Toth-Allen, Ph.D. Failure to respond and to implement corrective actions could result in enforcement action without further notice or the initiation of investigator disqualification procedures.

A copy of this letter has been sent to FDA, Baltimore District Office, 6000 Metro Drive, Suite 101, Baltimore, Maryland 21215. We request that a copy of your response also be sent to that office. If you have any questions, feel free to contact Dr. Toth-Allen at (301) 594-4723, ext. 141.

Sincerely yours,


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

cc: (purged copy)

[REDACTED]

Enclosures