



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

94759d

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

Via Federal Express

WARNING LETTER

MAY -7 2004

William E. Gannon, Jr., M.D.
Vice President, Clinical Affairs
Celsion Corporation
10220-L Old Columbia Road
Columbia, Maryland 21046

Dear Dr. Gannon:

This Warning Letter informs you of objectionable conditions found during a recent Food and Drug Administration (FDA) inspection at your firm. This letter also discusses your written response to the noted deficiencies and requests that you implement prompt corrective actions. The inspection took place during the period from December 9 through 18, 2003, and was conducted by Ms. Stephanie L. Shapley, an investigator with FDA's Baltimore District Office.

The purpose of the inspection was to determine if your firm's activities as the sponsor of the following studies: [REDACTED]

[REDACTED] and [REDACTED]
[REDACTED]

complied with applicable FDA regulations. The product investigated in these studies, the [REDACTED] is a device as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 321(h).

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

Our review of the inspection report prepared by the Baltimore District Office revealed violations of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions and Part 50 - Protection of Human Subjects. Ms. Shapley listed her findings on a Form FDA-483, "Inspectional Observations," and discussed these findings with you and several others at the conclusion of the inspection.

The deviations noted on the FDA-483, your written response to those deviations, and issues from our subsequent review of the inspection report are discussed below.

1. Failure to ensure proper monitoring of the studies [21 CFR 812.40 and 812.43(d)]

Under FDA regulations, a sponsor must ensure proper monitoring of each investigation and must select monitors qualified by training and experience to monitor the investigations in accordance with applicable FDA regulations. 21 CFR 812.43(d).

Examples of your failure to satisfy these requirements include, but are not limited to, the following:

- The Phase I investigation was not monitored.
- While the ██████████ study was initiated in ██████████, the ██████████ (pivotal) study in ██████████, with both studies completed by ██████████ there was no written monitoring plan for the studies, and Celsion's written Standard Operating Procedures (SOPs) for study monitoring were not approved until October 2003.
- Study monitors were not qualified by training and experience, as required. Neither of the two individuals who conducted monitoring visits for the ██████████ study had previous experience in clinical monitoring; one of the two monitors had no training in clinical trials prior to conducting independent monitoring visits.
- At least one clinical site requested an internal audit from their reviewing institutional review board (IRB) because they felt the study monitoring was inadequate. The requested audit was conducted in July 2003.

In your response to these observations, you indicated that Celsion had monitored the clinical investigations but acknowledged that your records did not fully reflect that this activity took place. Furthermore, you stated that SOPs have been prepared and in-house training has been initiated. Proper implementation of the SOPs and adequate training of your monitors should help to correct monitoring deficiencies. Please include copies of your SOPs addressing study monitoring in your written response to this letter.

2. Failure to ensure that the investigator agreement met the requirements of 21 CFR 812.43(c)

A study sponsor must obtain from each participating investigator a signed agreement that includes information specified in 21 CFR

812.43(c), such as a statement of the investigator's commitment to conduct the investigation in accordance with conditions of approval imposed by the reviewing IRB or FDA, supervise all testing of the device involving human subjects, and ensure that the requirements for obtaining informed consent are met.

Examples of your failure to satisfy these requirements include, but are not limited to, the following:

- There was no investigator agreement found for one clinical site.
- Of the fourteen existing investigator agreements, none included statements with respect to the investigator's commitment to conduct the investigation in accordance with IRB and FDA conditions of approval or to supervise testing of the device with human subjects.
- Seven investigator agreements did not include a statement of the investigators' commitment to ensure that the requirements for obtaining informed consent were met.

You responded that Celsion had integrated the investigator study conduct responsibilities with the clinical protocol, and that investigators would be required to sign the original protocol and each amendment. Based on your response, it is unclear if this will meet regulatory requirements for investigator agreements.

3. Failure to provide investigators with information they needed to conduct the investigation properly [21 CFR 812.40]

Examples of this failure include, but are not limited to, the following:

- There were inconsistencies between the protocol and case report forms. For example, the protocol required a minimum of [REDACTED] to be taken on the same day, but case report forms allowed the recording of only one set of measurements. After recent FDA inspections of investigators involved in your clinical trial that were conducted in December 2003 and January 2004, one site was cited for not conducting [REDACTED]. The site responded that this was due to confusion over exactly what procedures were required in the protocol. Likewise, another site was cited for not having records to show that a [REDACTED] was taken on the same day for each subject enrolled and randomized. Based on our December 2003 inspection of your firm, it does not appear that you have addressed this inconsistency.
- A report of prior investigations of the device was not provided to investigators who had not participated in the [REDACTED] study,

as required by 21 CFR 812.45. In your written response, you stated that written reports of study results will be provided to investigators. If implemented, this would address the deficiency. Please note that your SOPs should also reflect this change.

4. Failure to meet reporting requirements [21 CFR 812.150(b)(5)]

A sponsor must prepare and submit several types of reports specified in 21 CFR 812.150(b). For example, a sponsor must submit progress reports to all reviewing IRBs at least annually. You failed to satisfy this annual reporting requirement because you did not submit progress reports to each reviewing IRB.

According to your written response, Celsion was under the impression that the clinical investigators were responsible for submitting annual reports to the IRB. Clinical investigators are responsible for submitting progress reports to the sponsor, monitor, and reviewing IRB under 21 CFR 812.150(a)(3). However, a sponsor must also submit progress reports to all reviewing IRBs.

The above-described deviations are not intended to be an all-inclusive list of deficiencies found in your clinical study. When conducting clinical investigations of products regulated by FDA, it is your responsibility to adhere to each requirement of the Act and all applicable federal regulations.

Within 15 working days of receiving this letter, please provide additional written documentation of the corrective actions you have implemented or will implement to prevent the recurrence of similar violations in current and future studies. You need not re-submit SOPs that were collected during the inspection. However, you should submit new or revised SOPs that address the deficiencies observed during the inspection. Also, you should submit monitoring reports/follow-up correspondence for studies currently ongoing to illustrate how monitoring is presently being conducted and documented. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you.

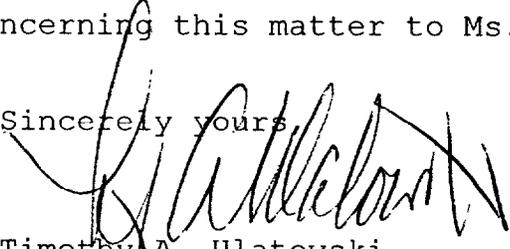
Send your response to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch I (HFZ-311), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Barbara Crawl.

A copy of this letter has been sent to FDA's 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.

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Please direct all questions concerning this matter to Ms. Crowl at
(301) 594-4720, ext. 168.

Sincerely yours,



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