DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

g1636d

Via Federal Express

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

WARNING LETTER

AUG 21 2001

Meredith Rigdon Lentz, M.D.
Lentz Apheresis Center
397 Wallace Rd, Suite 314
Nashville, TN 37211

Dear Dr. Lentz:

During the period of March 05 through May 10, 2001, Ms. Patricia S. Smith, an investigator from the Food and Drug Administration (FDA), New Orleans District Office, conducted an inspection at your facility. The purpose of this visit was to determine whether your activities as a sponsor/monitor and principal investigator of investigational studies of your apheresis devices complied with applicable FDA regulations. These studies included three Investigational Device Exemptions (IDEs) for your [redacted] for the treatment of [redacted] for the treatment of [redacted] and [redacted] for the treatment of [redacted] These products are devices as defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The inspection was conducted under a program designed, in part, to ensure that data and information contained in applications for Investigational Device Exemptions (IDEs) 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 the scientific investigations.

Our review of the inspection report submitted by the New Orleans District Office revealed serious violations of the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 812 - Investigational Device Exemptions, Part 50 – Protection of Human Subjects, and Section 520(g) of the Act. Inspectional observations were listed on the Form FDA-483 that was presented to and discussed with you and Ms. Jennifer Woods, RN, of your staff, at the conclusion of the inspection. We also acknowledge your May 22, 2001, written response to Ms. Smith that was forwarded to our office. That response addressed each of the inspectional observations cited.

The following discussion of violations is not intended to be all-inclusive of deficiencies encountered during our review of the inspection report and your response.

1. Failure to obtain FDA and/or Institutional Review Board (IRB) approval prior to allowing subjects to participate in research studies [21 CFR 812.20(a)(2), 812.40, 812.42, 812.110(a)]

FDA approved three IDEs for your [redacted]: one for the treatment of [redacted], a second for the treatment of [redacted], and a third for the treatment of [redacted]. There was no documentation that an IRB reviewed and approved the latter two IDE studies that were specific for [redacted] and [redacted].

You submitted a protocol, "[redacted]" to the Nashville Healthcare Network IRB 1/22/96 and it was approved 2/6/96 ([redacted]). However, you did not notify the IRB that FDA originally disapproved this protocol 1/17/96, nor that you had withdrawn this protocol for [redacted] from the IDE submission. In a letter to FDA, dated February 16, 1996, you confirmed this withdrawal. Nonetheless, you submitted a progress report/request for renewal to the IRB, dated 4/13/00, for a [redacted] in which you indicated that 8 subjects had been enrolled. However, it is unclear in what study these subjects had been enrolled.

You also submitted to the IRB the protocol, "[redacted]" on 1/22/96; IRB approval was 2/6/96. FDA did not grant conditional approval for this study until 3/1/96. You indicated in your response that although records do not establish that the IRB was notified of the conditional approval, no subjects had been enrolled until the IDE was approved.

You treated numerous patients "off-study" (i.e., not enrolled in the above-specified IDE studies) with your investigational device (s), using various protocols and consents that had not been submitted to and approved by FDA and/or IRBs. For example, patient [redacted] signed two different consent forms, "[redacted]" both dated 9/23/98. A claim was filed under "[redacted]" even though medical records indicate that the patient was suffering from [redacted]. Examples of consents signed and dated by these "off-study" patients were listed on the FDA 483.

In addition, since September 2000, you treated at least eight patients with your [redacted] prior to obtaining either FDA or IRB approval. To date, the [redacted] does not have an approved IDE. In your response to the Form FDA -483, you state that you consider your [redacted] to be a custom device. The Act's custom device definition, found in Section 520(b) of the Act, imposes five criteria, each of which must be met in order for the device to be considered to be a custom device. Your [redacted] does not meet any of these criteria, and therefore, is not a custom device.

Furthermore, under the IDE regulations 21 CFR 812.3(b), the definition for custom device includes a "specific form/special needs" condition. The special needs must relate to unusual anatomical features of the health professional or special needs of his or her practice that are not shared by other health professionals of the same specialty. Your use of the [redacted] does not fall under a "special need." Consequently, your [redacted] is subject to the IDE regulations.

In conclusion, your [redacted] - whether built by, or on the order of a physician; imported; or imported and modified, is not a custom device and must have an approved PMA or an IDE.

2. Failure to submit and obtain approval of a supplemental application prior to implementing a change to an investigational plan [21 CFR 812.35(a)]

You did not obtain prior FDA approval for changes in your investigational plan. This included your addition of study subjects and off-protocol use. For example, six subjects, rather than the five approved, were enrolled in your [redacted] Numerous additional patients were treated "off-study" with the investigational device(s).

During the [redacted], FDA approved the inclusion of two subjects ([redacted] who failed to meet the inclusion criteria. In a letter dated July 26, 1996, you informed FDA that subject [redacted] was not enrolled. In your response you stated that FDA and the IRB were informed of the substitution of [redacted] and you provided a clinical summary dated February 17, 1997. However, this summary does not constitute documentation that FDA was informed of and approved the substitution. You had informed the IRB that patients [redacted] and [redacted] were the FDA-approved exemptions, but for a [redacted] study. FDA did not approve a "general" [redacted] IDE and did not approve a substitution of [redacted] for the approved subject who had not been enrolled.

When FDA approves (conditionally or otherwise) an IDE for an investigational device, the device may be used to treat only the number of subjects approved in the IDE and only for the indications approved in the IDE. Treatments in number beyond the number of subjects approved in the IDE or treatments for indications not approved in the IDE are in violation of the conditions of approval of the IDE and the IDE regulations, and they adulterate the device under section 501(i) of the Act.

Your understanding that subjects could continue to be treated following their participation in the IDE is incorrect. The continued access memorandum to which you refer (#D96) covers the continued availability of an investigational device during the period between completion of the clinical study and FDA's approval of the marketing application. However, you were required to submit a request, in writing, as a supplement

to the IDE for an extended investigation and await FDA's determination whether to approve, approve with modifications, or disapprove the supplement. Your reference to a February 16, 1996, letter from you to FDA (response Exhibit 1) provides no evidence that FDA granted you permission to treat patients "off-protocol."

3. Failure to ensure that requirements for obtaining and documenting informed consent were met [21 CFR 812.100, and 50.20, 50.25, and 50.27(a)]

You failed to provide numerous subjects with adequate informed consent prior to allowing them to participate in an investigational study. For example, some of the consent documents were not specific to the condition under investigation (i.e., [redacted] and some had not been approved by an IRB. Some informed consents did not include all required elements, including identification of a contact person/phone number for questions regarding subjects' rights. Other consents had not been revised to include changes required or suggested by FDA. None were specific for costs that may be incurred by the subject from participation in the research.

Some of your patients signed consents to participate in unapproved and/or off-study protocols. The consents for your "off-study" patients were essentially the same as those given to IDE subjects. In fact, these consents indicated that the patients were participating in research studies and that the U.S. Food and Drug Administration and other government regulatory agencies could review their medical records. Also included were the following statements: "I understand that this is an investigational/experimental treatment for my disease;" " the physicians conducting the study will watch my physical condition and laboratory tests very closely while I am on the study;" "I understand that my participation in this research is voluntary;" and "freely give my consent to participate in this study." These statements imply, and lead the patients to believe, that they were participating in an FDA-approved IDE study. In your response, you claimed that some of the consents were signed in error by the patients.

Furthermore, for the unapproved [redacted]," patients signed a "Release and Covenant Not to Sue." This document included statements that the patient and spouse "covenant and agree not to institute or pursue legal proceedings or any other claim or action challenging the use of this new technology in my treatment." They also were asked to "forever waive all claims and complaints as a condition for being permitted to undergo treatment with this new technology." These statements contain exculpatory language and are prohibited under 21 CFR 50.20.

Not all of the reported six subjects enrolled in the [redacted] study signed a consent specific for [redacted]. The consents do not mention IRB review or identify

a contact for questions regarding subjects' rights. In addition, confidentiality is promised. Also, you failed to make corrections to the consent document as required in FDA's April 10, 1998, letter such as: "Before entering this study, the conventional methods of treating [redacted] have been explained to me and used in the treatment of my [redacted], however they have failed to prevent the spread of my disease;" "Other investigational methods of treating [redacted] have been explained to me and if I am accepted into this study, I agree to avoid these other forms of therapy;" and "I have had a [redacted] already, but I may need additional [redacted] when I am being considered for this study."

None of the subjects enrolled in the [redacted] study signed a consent specific for [redacted] The consent does not mention IRB review nor identify a contact for questions regarding subjects' rights. In addition, changes in the consent required by FDA for the [redacted] such as "I have had [redacted] already, but I may need additional [redacted] when I am being considered for this study," were not made.

During the [redacted], FDA approved the inclusion of two subjects who failed to meet the inclusion criteria. This was conditional on your amending the consent and obtaining IRB approval. You did not maintain documentation of IRB review/approval of an amended consent. In addition, signed consents for several subjects in this study were not available in subject files.

Consents to participate in the studies were often obtained after the [redacted] had been surgically placed in preparation for the [redacted]. You also signed some consents prior to the subjects/patients. This included the consent for patient [redacted] who was granted an exemption for the [redacted] by FDA on 6/13/96. The patient signed the consent 6/12/96 and you signed it 6/11/96.

4. **Failure to conduct the investigations in accordance with the investigational plan(s), other applicable regulations, and conditions of approval imposed by an IRB or FDA [21 CFR 812.100 and 812.110(b)]**

Some subjects were enrolled in your IDE studies even though they had not failed previous therapies, and some subjects received concurrent therapies during their [redacted] which were not reported to FDA.

For example, in the [redacted], some subjects received concurrent chemotherapy and/or radiation. In addition, several subjects had not failed any previous therapies such as chemotherapy, Interleukin 2, or Interferon ([redacted]. In the [redacted] at least five of the reported subjects received chemotherapy and/or other therapies concurrent with the [redacted]. Files for four of the six enrolled subjects lacked

documentation of [redacted] as per protocol inclusion eligibility criteria. In the [redacted] all four subjects received concurrent chemotherapy with their [redacted] Also, one subject in this study lacked a minimum of 21 days between receiving radiation and [redacted]

Some subjects also received multiple treatments, over varying time periods, which were not reported to either FDA or the IRB. In your response you stated that the clinical research protocols were limited to the initial treatment period (approximately 12 to15 treatments). You claimed that continued treatments were not under the protocol but were considered patient care under the practice of medicine. For your information, the "practice of medicine," found in Section 906 of the Act, pertains to the use of a legally marketed product for an indication not in the approved labeling. Your device is investigational and therefore does not fall under the "practice of medicine" provisions of the Act. All treatments associated with your [redacted] must comply with the requirements of the IDE regulations. Since the above noted treatments were not performed under an approved IDE, the data is not considered to be valid scientific data, and may not be accepted by the FDA.

5. **Failure to maintain accurate, complete, and current records relating to the investigations [21 CFR 812.140(a) and (b)]**

You failed to maintain adequate study records. For example, no case report forms (CRFs) or study rosters were completed for either the [redacted] studies. The limited CRFs available for the [redacted] were completed in 1999 although the study began in 1996. In some instances there was no source documentation to support clinical and laboratory data entered on CRFs.

There are discrepancies in patient rosters generated at your site when compared to information submitted to FDA and/or to the IRB. This included both the names and numbers of subjects in each study. In addition, you reported to the IRB that [redacted] and [redacted] were the FDA-approved exemptions for the [redacted] however, FDA did not approve [redacted] as an exemption and an IDE for general [redacted] was not approved.

Test article accountability records were inadequate. Records documenting the receipt, use and disposition of the device(s) were incomplete.

You also failed to maintain all submissions to, and correspondence with, the IRB including all records showing initial and/or continuing review. For example, there was no documentation that the IRB reviewed and approved the IDE protocols or consent documents specific to [redacted]

6. Failure to prepare and submit required reports [21 CFR 812.150(a)(1), (a)(4), and (b)(1)]

You failed to report all deaths/adverse events that occurred during the studies. For example, one subject ([redacted]) in the [redacted]tudy arrested immediately following the [redacted] procedure (10/26/99). Another subject ([redacted]) in th[redacted]study had a spontaneous cardiac arrest on 5/5/98. Neither of these deaths was reported to FDA or the IRB. You claimed that these events had been reported, and provided autopsy reports and progress notes with your response. However, these documents do not show that the information had been previously submitted to FDA.

7. Failure to have adequate written monitoring procedures, select qualified monitors, and monitor the clinical investigations in accordance with 21 CFR 812.25(e), 812.40, and 812.43(d)

You had no written procedures for study monitoring or data handling for any of the studies. Procedures provided with your response included those for infection control, materials handling (e.g., blood and chemicals), incident reporting, and others. There were no procedures related specifically to your monitoring of investigational studies.

You state in your response that you have hired the consulting firm [redacted] to update the format and content of all standard operating procedures involving the conduct of clinical trials, and that all personnel associated with the conduct of clinical trials will be trained in these new procedures. Please be aware that written procedures for monitoring each investigation are required to be included in your IDE application.

As a sponsor of investigational studies, you are required to ensure compliance with all applicable federal regulations. You stated that you served as study monitor for the three IDE studies because the IDEs were conducted at a single site; however, you failed ensure compliance with applicable requirements. With regard to monitoring the drug studies you conducted, you state that monitoring of patients is done by recording patients' progress in their patient charts. This activity does not fulfill requirements for monitoring.

In addition to the serious deficiencies associated with the investigational device studies you conducted, there were deficiencies associated with your conduct of investigational drug studies. You failed to assure that the trials were conducted according to the protocols as submitted to FDA and per the regulations. For example, some subjects who were enrolled were never seen at your clinic, and the protocol was not followed for follow-up visits. Drug accountability and disposition records were inadequate, as was study monitoring. Some subjects signed consents for one study that referenced a local IRB chairman; however, this IRB had disapproved the study.

As discussed above, significant deficiencies relating to your conduct of clinical investigations of products regulated by the FDA, both device and drug, were observed during the inspection. As both a sponsor and clinical investigator of products regulated by the FDA, it is your responsibility to ensure that all regulatory requirements are met.

Within 15 working days of receipt of this letter, provide this office with the following information:

For each of the three IDE studies, you stated that all required annual and final reports have been provided to the IRB for each study. Provide documentation that 1) those reports were specific to each IDE under study, and 2) that they were submitted for review within the timeframe established by the IRB. Was the same information provided to the IRB and FDA in your reports? If not, explain. In addition, if you have documentation that changes/modifications to any of the studies were submitted to and approved by the IRB, provide this information as well.

Because there were discrepancies noted in the identification of study subjects in the information provided to FDA, the IRB, and the roster provided by your site, please provide an accurate listing of the subjects in each study. If subjects/patients were included in more than one study (including your [redacted] study), please identify them.

You stated in your response that no patients are being recruited into studies at your Apheresis Center because enrollment limits were met for the three IDE studies. Please provide assurance that no further patients will be treated with any of your investigational devices.

Some study subjects received numerous cycles of your investigational [redacted] treatments. You stated that only the initial treatments were done under the IDE. Please clarify, for each subject, exactly what information was reported to FDA and the IRB regarding the initial and subsequent treatments. If previous or subsequent treatments for study subjects were not reported, explain your rationale for not reporting that information.

It does not appear that protocols specific to [redacted] and [redacted] were submitted to and approved by the reviewing IRB. If this is not the case, please provide documentation of approval of these specific studies. If protocols specific to these [redacted] were not approved by the IRB, how was data from these studies reported to them? (i.e., under which study)? For example, a 4/13/00 report to the IRB indicated that eight subjects were enrolled in the [redacted] study; however, FDA had not approved an IDE for general [redacted]

Describe your procedure for handling complaints. If complaints were received concerning your investigational treatments, were FDA and the IRB notified?

Provide your newly implemented written procedures for monitoring investigational studies of products regulated by the FDA. Because you stated in your response that enhanced recordkeeping procedures would be instituted, include these procedures in additional to those for reporting adverse events.

In your Curriculum Vitae under the heading, "Present Positions (Aug 1997-Present)," you indicated that you are a principal investigator at the Sarah Cannon Cancer Center. However, in your response you stated that you opened your private practice under Lentz Apheresis Center that reportedly has no connection with the Sarah Cannon Cancer Center. Please explain.

Your response should be directed 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: Liliane Brown. If you need additional time to respond, contact Ms. Brown for an extension. Failure to respond may result in regulatory action without further notice, including initiation of investigator disqualification procedures. Continued use of unapproved devices may result in seizure.

A copy of this Warning Letter was sent to the Food and Drug Administration's New Orleans District Office, 6000 Plaza Drive, Suite 400, New Orleans, Louisiana 70127. We request that a copy of your response also be sent to that office.

Please direct all questions concerning this matter to Ms. Brown at (301) 594-4720, ext. 136.

Sincerely yours,

for Larry D. Spears
Acting Director
Office of Compliance
Center for Devices and
Radiological Health

cc: PURGED COPIES

1. Medical Board of California
Central Complaint Unit
1426 How Avenue
Sacramento, CA 95825

2. Composite State Board of Medical Examiner
Attn: Ms. Gladys Henderson, Complaints Unit
2 Peachtree Street, NW, 10th floor
Atlanta, GA 30303

3. Department of Health
Office of Investigations
Third Floor Cordell Hull Building
425 Fifth Avenue North
Nashville, TN 37247

4. Ben W. Davis, M.D. IRB Chairman
Columbia, Nashville Division IRB
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5. Mark Sims, Administrator
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5. Paul Rutledge, President
TriStar Nashville Market
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6. Western IRB
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