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

OCT 14 2005

WARNING LETTER
VIA FEDERAL EXPRESS

Debra E. Weese-Mayer, M.D.
Director, Pediatric Respiratory Medicine
Rush University Medical Center
1653 West Congress Parkway
Kellogg 726
Chicago, IL 60612

Dear Dr. Weese-Mayer:

The purpose of this Warning Letter is to inform you of objectionable conditions revealed during a Food and Drug Administration (FDA) inspection of your clinical site and to request a prompt reply. During the period of June 17 through July 13, 2005, an investigator from FDA's Chicago District Office inspected your site. The purpose of the inspection was to determine whether your clinical site's activities and procedures relating to the investigational study of the [REDACTED] complied with applicable FDA regulations. The [REDACTED] is a device as that term is defined in Section 201(h) of the Federal Food, Drug, and Cosmetic Act (Act) [21 U.S. C. 321(h)].

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

We have completed our review of the report submitted by the Chicago District Office that described and documented deviations from the requirements of Title 21, Code of Federal Regulations (21 CFR), Part 50 - Protection of Human Subjects, and Part 812- Investigational Device Exemptions. These deviations were listed on the Form FDA 483, "Inspectional Observations," that was presented to and discussed with you at the conclusion of the inspection. The deviations noted on the Form FDA 483 and our

subsequent review of the inspection report are discussed below:

Failure to obtain proper informed consent prior to any study related procedures. [21 CFR 50.20, 50.27(a), 812.100, and 812.140(a)(3)(i)]

Investigators are responsible for ensuring that informed consent is obtained prior to any study related procedures using an IRB-approved consent and that records of informed consent are kept in accordance with FDA regulations. Our investigation revealed several incidences of failure to obtain IRB-approved informed consent prior to study procedures. The following are some examples:

- 1) Subject [REDACTED] was [REDACTED] on September 15, 1992. The IRB-approved consent document was signed by Dr. [REDACTED] on September 14, 1992. However, the [REDACTED] did not sign the consent until January 31, 1993.
- 2) Subject [REDACTED] was [REDACTED] on April 7, 1992, prior to IRB approval of the investigation on April 20, 1992. A general informed consent document was signed on April 7, 1992. However, [REDACTED] did not sign the IRB approved consents until [REDACTED] was performed on October 24, 1994, and April 15, 1996.

Failure to conduct the investigation according to the signed agreement, the investigational plan, and applicable FDA regulations. [21 CFR 812.100 and 21 CFR 812.110(b)]

It is the responsibility of the investigator to conduct the investigation in accordance with the signed investigator agreement, investigational plan, and applicable FDA regulations. Several examples of failures to conduct the investigation in accordance with the investigational plan are listed below:

You failed to report serious adverse effects in accordance with the investigational plan and the approving IRB's policy. The investigational plan required reporting of serious adverse effects to the sponsor and IRB within ten working days after first learning of the effect. Additionally, the IRB policy requires reporting of serious adverse effects within seven days and within fifteen days for unexpected adverse experiences and unanticipated problems. Examples of this failure include, but are not limited to, the following:

- 1) [REDACTED] died in May 2004 for which the cause is [REDACTED]. The site was notified by the [REDACTED] at the time of the death. However, it was not reported to the IRB or sponsor, despite the investigational plan and IRB policy, until the FDA inspection in July 2005.
- 2) [REDACTED] died in February 2005 of [REDACTED]. The site was notified by the [REDACTED] at the time of death. However, it was not

reported to the IRB or sponsor, despite the investigational plan and IRB policy until the FDA inspection in July 2005.

You failed to complete diagnostic tests and procedures in accordance with the investigational plan. Examples of this failure include, but are not limited to, the following:

- 1) Pre-operative assessment for patients with [REDACTED] requires confirmation of [REDACTED] normality, and confirmation of [REDACTED] using standard conditions under fluoroscopy if damage to [REDACTED] expected. Two subjects at the site with [REDACTED] did not receive this assessment.
- 2) Post-operative assessment study flow chart 1 and 2 requires that checking currents and adjusting parameters be conducted post-operatively at week 1, day 14, and as needed. These assessments were not performed in accordance with the investigational plan for subjects, [REDACTED]

Failure to submit progress reports on the investigation to the sponsor, the monitor, the reviewing IRB at regular intervals, but in no event less often than yearly. [21 CFR 812.150(a)(3)]

It is the responsibility of the investigator to submit progress reports to the reviewing IRB at regular intervals, but in no event less often than yearly. However, you failed to obtain continuing review and approval of the investigation from the IRB from April 1993 through April 1994 and you submitted the 1997 review 2-1/2 months late.

Failure to maintain accurate, complete, and current case histories. [21 CFR 812.140(a)(3)]

An investigator is responsible for maintaining accurate, complete, and current records of each subject's case history and exposure to the device, which includes the case report forms and supporting data. You failed to maintain accurate, complete, and current case histories. Examples of missing case report forms (CRFs):

- 1) Registration Forms A and B for the following subjects: [REDACTED]
- 2) Registration Form B for the following subjects: [REDACTED]

Failure to maintain records of device receipt, use, and disposition. [21 CFR 812.140(a)(2)]

Investigators are responsible for maintaining records of receipt, use, or disposition of a device that relate to the following: type and quantity of the device; dates of its receipt;

batch number or code mark; names of all persons who received, used, or disposed of each device; and why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of. However, you began implanting devices in April 1992 and you failed to maintain the aforementioned records from 1992 to June 2005.

The above-described deviations are not intended to be an all-inclusive list of deficiencies that may exist in this clinical study. It is your responsibility as a sponsor to assure adherence to each requirement of the Act and all applicable federal regulations.

You submitted a request to the IRB to treat a patient as a compassionate exemption. Please note, the compassionate use of investigational devices allows access for patients who do not meet the requirements for inclusion in the clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their disease or condition. FDA recognizes that there are circumstances in which an investigational device is the only option available for a patient faced with a serious, albeit not life-threatening, disease or condition. A physician should not treat the patient until FDA approves use of the device under the proposed circumstances for that subject. For additional information on compassionate use:

<http://www.fda.gov/cdrh/devadvice/ide/early.shtml#compassionateuse>

Within **15 working days** after receiving this letter please provide copies of policies, procedures, and training with expected completion dates that you have developed and implemented to ensure these deviations are corrected and will not occur in the future. In addition, please provide a list of your current investigational studies and include the name of the study sponsor and the date of IRB approval. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. 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 21 CFR 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/>. Send your response to: Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Special Investigations Branch, HFZ 311, 9200 Corporate Blvd., Rockville, Maryland 20850, Attention: Doreen Kezer.

We are also sending a copy of this letter to FDA's Chicago District Office, and request that you also send a copy of your response to that office. If you have any questions, please contact Ms. Doreen Kezer by phone at 240-276-0125 or by email at DMK@cdrh.fda.gov.

Sincerely yours,



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

cc.

