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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

Via Federal Express

DEC 3 1999

WARNING LETTER

Joseph L. Moerschbaecher, Ph.D.
Vice Chancellor for Academic Affairs
Louisiana State University
Medical Center
433 Bolivar Street, Room 206
New Orleans, Louisiana 70112-2223

Dear Dr. Moerschbaecher:

During the period of August 23 through September 7, 1999, Ms. Dana M. Daigle and Ms. Barbara D. Wright, investigators from the Food and Drug Administration's (FDA) New Orleans District Office, visited the Institutional Review Board (IRB) at Louisiana State University Medical Center. The purpose of this visit was to determine whether your procedures complied with Title 21, Code of Federal Regulations (21 CFR), Part 50-Protection of Human Subjects, Part 56-Institutional Review Boards and Part 812 – Investigational Device Exemptions. These regulations apply to clinical studies of products regulated by the FDA.

Serious deviations were noted during the inspection. These deviations were listed on form FDA-483, "Inspectional Observations," which was presented to and discussed with Dr. M. Wayne Hurst, the IRB Chair, at the conclusion of the inspection. Also present for this discussion were Dr. Kenneth E. Kratz, IRB Vice-Chair, and [redacted] Our review of the inspection report revealed the following deficiencies:

- Re-approvals are not receiving the proper review and approval of the IRB committee. Presently, the IRB Chair approves most re-approvals, regardless of the nature of the study, via expedited review procedures, and the names of these studies are then printed in the monthly report as a listing of studies that have been re-approved. The committee votes to approve the monthly review as a total package. Re-approval forms that arrive too late for the monthly review are read aloud at the meeting by the coordinator and voted on as a group. 21 CFR 56.110(b) defines specific studies that may be reviewed via expedited review. According to 21 CFR 56.108(c), except when an expedited review is allowed, review of research is to occur at a convened meeting of the IRB at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. To be approved, research must receive the approval of a majority of those members present.

- Changes in protocol and changes in consent forms are not properly reviewed by the committee. These are listed in the monthly report that is voted on as a package, without discussion. According to 21 CFR 56.108(a)(4), changes in approved

research may not be initiated without IRB review and approval. Unless these changes fulfill the requirements for expedited review, this review should be the same as for new studies and re-approval, as required by 21 CFR 56.108(c).

- Adverse event reports are not properly reviewed. They are initially received by the Chair and listed in the monthly report without description of severity. They are voted on as part of the monthly package, without specific discussion. Regulations cited above regarding review of changes to protocol and informed consent apply.

- Re-approval forms are not dated when signed/stamped with the Chair's signature and stamped signatures are not properly initialed. Moreover, approval letters do not instruct investigators of the responsibilities regarding restriction of subject enrollment if IRB approval has elapsed prior to notice of re-approval. 21 CFR 56.109 requires that an IRB inform investigators of their decisions in writing (section c) and that continuing review occur no less than once a year (section f). It is therefore essential to inform clinical investigators of the date of re-approval, the determined interval for continuing review, and the consequences of lapsed approval.

- Several re-approval times extend beyond the maximum one-year period, as the initial approval date is consistently used for determination of the re-approval time frame, even when re-approval occurs early. 21 CFR 56.109(f) requires an IRB to conduct continuing review at intervals appropriate to the degree of risk, but not less than once per year.

- IRB standard operating procedures, which are contained in your IRB Guidebook, do not cover all the required functions and operations of an IRB. Specifically:

  - Procedures for reviewing and determining the significant risk/non-significant risk status of investigational device studies are not included. According to 21 CFR 812.66, if an IRB determines that an investigation, presented for approval as a non-significant risk device study, involves a significant risk, it must notify the investigator, and where appropriate, the sponsor.
  - There are no procedures for tracking studies approved for less than one year. According to 21 CFR 56.108(a)(2), an IRB must follow written procedures regarding continuing review, which is to be conducted no less than annually.
  - There are no procedures to ensure prompt reporting to the IRB and to the FDA of unanticipated problems, serious or continuing non-compliance, or suspension or termination of a study. These are required by 21 CFR 56.108(b).
  - There is no description of the use of sub-committees, even though meeting minutes often reference approval pending sub-committee review. 21 CFR 56.108(a)(1) requires written procedures for conducting reviews of research.
  - There are no procedures for the handling of expedited reviews. Expedited review is a procedure for conducting review of research and therefore requires written procedures, as cited above.

  - It is stated that the IRB Chair is responsible for "annual" re-approvals, regardless of the nature or risk associated with the study. Review by an individual IRB member or the IRB Chair, without concurrence of the committee, is expedited review, which is reserved for initial and continuing review only of studies that meet the requirements of 21 CFR 56.110(b).

- The edition of the IRB Guidebook presently in use is dated 1994 and does not include the present procedures for the primary reviewer system, the reviewer checklist, re-approval procedures, and serious adverse event handling. As previously cited, 21 CFR 56.108(a)(1) requires that an IRB follow written procedures for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution.

- Meeting minutes are deficient in that:
  - Discussion of controverted issues is not included, neither a summary of the discussion nor the resolution determined. 21 CFR 56.115(a)(2) requires meeting minutes to be in sufficient detail as to include a written summary of the discussion of controverted issues and their resolution.
  - Vote tallies are not always recorded. Moreover, some vote tallies do not agree with the number of voting members listed as present. 21 CFR 56.115(a)(2) requires meeting minutes to include the number of members voting for, against, and abstaining.
  - Clinical investigators listed as present are not specifically noted as abstaining from voting on their own studies. According to 21 CFR 56.107(e), no IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.
  - Members of sub-committees referenced are not identified. Identification of sub-committee members is necessary to assure they are qualified to serve as chosen. (Their qualifications could be determined from the list of IRB members, with pertinent information regarding their qualifications for service, maintained in IRB records as required by 21 CFR 56.115.)

The deviations listed above are not intended to be an all-inclusive list of deficiencies. The IRB is responsible for adhering to each requirement of the law and relevant regulations.

We acknowledge receipt of a copy of your response to Mr. Richard Debo, New Orleans District Office, dated September 24. Your letter promises to modify the procedures for continuing review, including the time frame, method of performing continuing review, and notification to investigators of the period of approval. Moreover, you attached a copy of a notice to be included in all letters reminding investigators that their periodic review is imminent and cautioning them that research enrollment is to be suspended if their present approval expires before re-approval. This notice states that the "annual

renewal form" is attached. Since periodic review of research can occur in a shorter time frame, this wording should be amended to be inclusive of other time frames.

Your letter also promises a revision in the methods for reviewing reported adverse events and for recording and presenting meeting minutes. You state that the IRB Guidebook will be modified to omit the statement that the Chair must review all annual renewals and to include procedures for handling significant risk/non-significant risk decisions with regard to investigational device studies. This IRB Guidebook revision was to be initiated in October.

In two instances your letter references materials related to the Office for Protection from Research Risks (OPRR). These references include your response that the IRB Guidebook does contain procedures for ensuring prompt reporting of unanticipated events, as well as your attachment of an OPRR letter regarding the practice of maintaining the initial date of approval as the continuing review date. OPRR enforces the IRB regulations in 45 CFR Part 46. As stated above, FDA IRB requirements are mainly found in 21 CFR Part 56. If your IRB reviews and approves studies under the jurisdiction of the FDA, specific references to all 21 CFR Part 56 requirements need to be included in the IRB Guidebook.

The promises of modifications in your response include those that the FDA requires from IRBs working to comply with the regulations. However, we have received those promises from your IRB in the past, after inspections in both 1992 and 1993, and yet FDA's recent inspection revealed that major deficiencies remain. Moreover, the inspectional report notes that the IRB reviews a large volume of data in relatively short time frames and that student workers are required to properly handle the volume of renewal forms that consistently arrive. Implementation of the proper procedures for continuing review and the review of changes and adverse effect reports may therefore require changes in the size or functioning of the committee as presently constituted.

Please inform us as to how the IRB plans to effectively implement the changes proposed. Moreover, since these changes were to go into effect in September, please include copies of the minutes of IRB meetings held since revisions were instituted. If specifics regarding the procedures for continuing review of studies included are not specified in the minutes, please include a description of those as well. This would include the procedure for choosing the primary reviewers, their qualifications, and the reasons for limited or extended discussion of a study at the meeting. If adverse effects and/or study changes were not discussed during the recent meetings, please include the procedures that have been developed for reviewing these as well. Also include a copy of the revised IRB Guidebook or indicate when this copy will be made available if still in revision.

Please send the information requested above, within 15 working days of receipt of this letter, 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 could result in further regulatory action, including, as described in 21 CFR 56.120 and 56. 121, withholding approval of new studies, directing that no new subjects be added to on-going studies, terminating on-going studies, notifying relevant State and Federal regulatory agencies, and disqualification of the IRB.

Copies of 21 CFR Parts 50 and 56, the November 9, 1998 Federal Register notice titled "Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure," as well as the FDA Information Sheets are enclosed to assist you. Also enclosed is a copy of 21 CFR 812.66. This section of the Investigational Device Exemption (IDE) regulations describes an IRB's responsibility regarding the non-significant risk/significant risk status of an investigational device study.

A copy of this letter has been sent to FDA's New Orleans District Office, Textron Marine Systems Plaza, 6600 Plaza Drive, Suite 400, New Orleans, Louisiana 70127. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Jean Toth-Allen at (301) 594-4723, ext. 141.

Sincerely yours,

for Lillian J. Gill
Director
Office of Compliance
Center for Devices and Radiological Health

Enclosures

cc:
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Institutional Review Board

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