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Warning Lettervia Federal ExpressFood and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850Patrick Quinlan, M.D.
Chief Executive Officer
Ochsner Clinical Foundation
1514 Jefferson Highway
New Orleans, Louisiana 70121

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Dear Dr. Quinlan:

The purpose of this letter to inform you of objectionable practices and activities found during a Food and Drug Administration (FDA) inspection of the Clinical Investigations Committee (CIC), an Institutional Review Board (IRB), of Ochsner Clinical Foundation and to request corrective actions. The inspection took place during the period of November 5-28, 2001, and was conducted by Ms. Dana M. Daigle, an investigator from FDA New Orleans District Office, and Ms. Marian Linde-Serge, a Nurse Consultant from FDA's Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring.

The purpose of the inspection was to determine whether the IRB's activities and procedures for the protection of human subjects complied with applicable federal regulations. These regulations and observations apply to clinical studies of all products regulated by the FDA.

We reviewed the observations, documents, and records contained in the establishment inspection report (EIR) resulting from this inspection. Our review of the information reveals violations of FDA regulations contained in Title 21, Code of Federal Regulations (21 CFR), Part 50 – Protection of Human Subjects and Part 56 – Institutional Review Boards.

Ms. Daigle listed her observations on the form FDA-483, "Inspectional Observations," which, at the conclusion of the inspection was presented to and discussed with Dr. Carl Kardinal, CIC Chair, at the conclusion of the inspection. Dr. William Pinsky, Dr. Richard Re, Dr. George Pankey, Ms. Wendy Portier, Dr. Claire Dunne, and Ms. Denise Pinkston were present during the presentation and discussion of the FDA-483. A copy of the FDA Form-483 is enclosed for your reference.

We acknowledge receipt of copies of two letters from Drs. Re, Kardinal, and Dunne (letters were dated December 17, 2001, and January 21, 2002) that were sent to the New Orleans District Office in response to the inspectional observations. These letters will be made a part of our official files. The letters describe the following: the contract with

Western Institutional Review Board (WIRB) to perform initial and subsequent review of all future externally funded trials and some intramural generated protocols; that Ochsner Clinical Foundation CIC will perform review of already approved research and selected new intramural protocols; and the CIC will review all standard operating procedures. These activities are inadequate given the extent of the noncompliance at the institution. The corrective action plan neither addresses the review of previously approved investigations nor the positive steps that the CIC must put into practice to comply with all pertinent federal regulations for the protection of human subjects in research.

This letter informs you of the violations found during the recent inspection. Many of these violations were observed and brought to Ochsner's attention during past FDA inspections. Previous commitments to correct these violations have not been implemented. For your review and reference, we have enclosed copies of previous FDA Form 483's for the following dates: May 3, 1994; November 20, 1997; September 21, 1999; and November 28, 2000.

The violations listed below are not intended to be an all-inclusive list of deficiencies. As the parent institution, the Ochsner Clinical Foundation is responsible for ensuring that the CIC adheres to each requirement of all pertinent federal regulations.

1. Failure to have adequate written procedures for conducting initial or continuing review of research per 21 CFR Part 56, Subpart C.

The regulations require IRBs to adopt and follow written procedures for conducting their review of research. The institution's procedural manual entitled "The Alton Ochsner Medical Foundation, Division of Research Policy Manual," revised July 2001, does not meet all regulatory requirements.

The manual does not adequately describe the criteria for review of research and information. For example, it does not adequately, 1) cover all required functions and operations of the CIC, 2) address how the institution is notified of CIC findings and actions, and 3) describe expedited review or emergency research.

Also, the manual does not contain written procedures delineating the role and responsibilities of CIC members assigned as primary and secondary reviewers or the role and responsibilities of CIC members on specialized institutional or CIC review committees. The manual does not contain work instructions or directives, including maintaining reports and records necessary in the performance of the Biosafety, Radiation, Gene Therapy, and other specialized groups, whose review precedes CIC review. In addition, there are no procedures describing the responsibilities of Chairperson as a tertiary reviewer.

The manual does not adequately describe how the CIC support staff prepares and maintains records of all IRB activities, including meeting minutes, records and reports associated with investigations, and archiving. The manual does not describe how data and information are gathered, stored, and analyzed to prevent research misconduct. Also, the manual does not describe how electronically stored data and information are safeguarded and maintained.

In addition, the manual does not have procedures for how the CIC determines whether an investigational medical device study is a significant risk or non-significant risk device study as required in 21 CFR 812 – Investigational Device Exemption (IDE) regulations.

The CIC manual must accurately describe the functions and operations of the CIC. The procedures must provide all information that employees need to perform their tasks correctly. Terminology used in written procedures should approximate as closely as possible regulatory terms in order to avoid confusion. For example, laypersons should not be described as “anyone other than physicians,” administrative review should not be used to describe expedited review, and compassionate use should not be used to describe emergency use.

In addition, all procedures in the manual should be reviewed on a regular basis for needed changes and to ensure the CIC is properly implementing all procedures. The CIC should ensure there are standard operating procedures for continuous quality assurance of the review of the manual. Outdated procedures in the manual should be updated or replaced, but historical copies of all manuals should be maintained by the CIC and accessible during internal audits and FDA inspections.

2. Failure to conduct review of research as described in the written procedures and required by 21 CFR 56 Subpart C.

The manual states alternate members may participate in the meeting only when it is necessary to maintain a quorum. A quorum is defined by the institution as 50 percent of the CIC (regular) membership plus one more regular member. A review of your meeting minutes reveal alternate members participated contrary to this procedure at the following nine meetings: February 19; April 23; May 28-29; June 26; July 23; August 27; and September 24-25, 2001.

It is not apparent that the CIC conducts full review of research at their convened meetings. The CIC does not review, discuss, and vote on individual continuing review research projects, including protocol amendments, changes, and adverse events. At the September 24, 2001, CIC meeting 93 studies were reviewed within 55 minutes. The record for this CIC meeting indicated 25 continuing reviews, 30 local adverse events, and 21 study changes were reviewed, discussed, and voted on during the convened meeting. However, a substantive and meaningful review (discussion and vote on each protocol) apparently did not occur for each continuing research project.

Our review of other CIC meetings minutes noted similar review time frames, that is, the reviews of numerous studies completed within a span of one hour. For example, the August 27, 2001, meeting minutes recorded the review of 210 studies in 50 minutes; the May 28, 2001, minutes recorded the review of approximately 200 studies in 60 minutes; and the February 19, 2001, minutes recorded the review of approximately 200 studies in 55 minutes.

Our review of the CIC records revealed that the CIC apparently does not review complete study files when significant protocol changes and safety information are submitted to the CIC for review. For example, during the January 23, 2001, meeting, the CIC approved

 for another year without discussing numerous Investigational New Drug (IND) Safety Reports, including , and which the minutes recorded that the CIC had "No Comment." The sponsor terminated this study two months later.

3. The IRB fails to prepare and maintain adequate documentation of IRB activities as required by 21 CFR 56 Subpart D.

Documentation of the CIC membership and its roster is inadequate in that it does not identify those who are knowledgeable in regulations, institutional commitments, applicable law, and standards. The CIC MEMBERSHIP roster does not identify the primary member(s) for whom each alternate member may substitute. Also, training records of members are not available.

The CIC meeting minutes do not accurately reflect the activities of its meetings. Votes and discussions at convened meetings do not occur as documented. For example, none of the 68 studies listed under the Major Revision, Minor Revision, Ongoing Reviews, and Adverse Events section of the meeting minutes were reviewed, discussed, and voted on individually as reported in the September 24, 2001, meeting minutes.

The vote on the CIC reviews is inconsistent with regulations and often fails to record the number of members voting for, the number voting against, and the name of the member(s) who abstains.

The CIC correspondence to the clinical investigator does not accurately reflect the review and approval activities that take place during the CIC meetings. Also, the CIC's review of IND Safety Reports and non-local adverse events is inconsistent and not accurately reflected in correspondence to the institution and the clinical investigator. For example, the CIC notified the clinical investigator that it reviewed 35 IND Safety Reports during the September 24, 2001 meeting, when in fact, there is no record that these safety reports were discussed at the meeting.

The CIC fails to maintain all regulatory information related to a research project. For example, the CIC approved a research project even though there were concerns among institution officials that an Investigational New Drug Application (IND) may be needed. For example, there are no records that document that Dr. Steven Ramee submitted an IND for his study that the CIC approved. The title of the research project is

[REDACTED]

The Division of Cardio-Renal Drug Products, Center for Drug Evaluation and Research, determined that the above study requires an IND. Therefore, it is necessary that an IND be obtained from FDA in order for this study to be legally conducted. An IND application for this study must be sent to the Food and Drug Administration, Center for Drug Evaluation and Research, Central Document Room, 12229 Wilkins Avenue, Rockville, MD 20852-1833. Information on the preparation and submission of an IND are available online at <http://www.fda.gov/cder/forms/1571-1572-help.html>. Copies of the IND regulations, further guidance regarding IND procedures, and additional forms are available from the FDA Center for Drug Evaluation and Research, Drug Information Branch (HFD-210), 5600 Fishers Lane, Rockville, Maryland 20857, telephone (301) 827-4573 or toll free at 1-888-INFOFDA.

During the inspection, Ms. Daigle and Ms. Linde-Serge inquired whether Ochsner was conducting gene therapy research. Dr. Kardinal informed them that the institution does not conduct gene therapy research. As CIC chairperson, Dr. Kardinal reviews all submissions to the CIC regardless of the nature of the study and presides over the CIC convened meetings. However, the Division of Clinical Trials, Designs, and Analysis, Office of Therapeutics Research and Review, Center for Biologics Evaluation and Research at the FDA advised this office that the

[REDACTED] is an example of gene therapy research.

FDA's administrative actions

The FDA holds the parent institution accountable for the CIC's functions and operations with respect to review and approval of biomedical research regulated by the FDA and for the protection of the rights and welfare of human subjects in research. We are concerned that the CIC's activities and operations are not adequate to protect the rights and welfare of human subjects in research.

Because of the serious noncompliance with FDA's regulations, we request you immediately contact this office to arrange a meeting or telephone conference to discuss corrective actions. You should be sufficiently represented at the meeting by members of your institution's human subject protection programs, including responsible institutional advisory members, or consultants of your choosing.

Your failure to arrange this meeting may result in alternative administrative action, under the authority of regulations at 21 CFR 56.120 (b), (1), and (2), including the immediate suspension of Ochsner Medical Foundation CIC's authority to:

- approve new research studies of FDA-regulated products subject to 21 CFR Part 56 (This includes all studies regulated by the FDA under sections 505(l) and 520(g) of the Food, Drug, and Cosmetic Act as well as any clinical investigations that support applications for research and marketing permits.) See 21 CFR 56.101 and 56.102;
- add new research subjects to ongoing FDA regulated studies (21 CFR Part 56); and
- continue ongoing studies subject to 21 CFR Part 56 when doing so would not endanger the subject.

During the meeting, Ochsner Medical Foundation representatives must be prepared to discuss a corrective action plan that includes at a minimum the following items:

- a satisfactory plan to ensure that all previously approved investigational studies are adequately reviewed in accordance with FDA requirements, including the applicability of an IND or IDE submission
- revision of current CIC policies and procedures so that the functions and operations in the manual comply with all pertinent federal regulations (include the date of revision, and signatures of approval officials, and the date of implementation)
- a satisfactory plan to ensure that all CIC members and staff are appropriately educated, on a continued basis, about the regulatory requirements for review of research projects and the protection of human subjects
- a satisfactory plan to ensure that the CIC (or the institution) prepares and maintains adequate documentation of the CIC activities
- full disclosure of any use of non-approved therapies or approved therapies used for indications other than approved (off-labeled use). Identify the product, the physician, the patient medical record number, the reason for the use of product, and any adverse events including deaths that occurred after use of the product(s) regardless of causality and in any patients who received the product(s)

Further, in order to comply with your DHHS Assurance, you must also include all requirements found in 45 CFR 46 in the CIC's policy manual. For assistance with these regulations you should call a representative in the Office for Human Research Protections (OHRP) at (301) 402-5552.

Within fifteen (15) working days of receipt of this letter, you must contact Mr. David R. Kalins, Branch Chief, Division of Bioresearch Monitoring, Office of Compliance, Center for Devices and Radiological Health at (301) 594-4723 to arrange for a meeting. Failure to respond may result in regulatory action without further notice as previously described.

Sincerely yours,



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

Enclosures

cc:

