DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

g3840d

Via Federal Express

FEB 27 2003

WARNING LETTER

Robert W. Rubin, Ph.D.
President/CEO
Lovelace Respiratory Research Institute, Inc.
5400 Gibson Boulevard, Building 20
Albuquerque, New Mexico 87108

Dear Dr. Rubin:

The purpose of this letter is to inform you of objectionable practices and activities found during a Food and Drug Administration (FDA) inspection of the Lovelace Institute Institutional Review Board (IRB), which serves as the IRB for your institution, and to request corrective actions. The inspection took place during the period September 9-13, 2002, and was conducted by Ms. Cynthia Jim, an investigator from FDA's Denver District Office, and Ms. Barbara Crowl, a Consumer Safety Officer from FDA's Center for Devices and Radiological Health.

The purpose of the inspection was two-fold. First, it was to determine whether the IRB's activities and procedures comply with applicable federal regulations. The regulations apply to your oversight of clinical studies of all products regulated by the FDA. Second, it was to determine whether or not corrections had been made to address deficiencies identified in a June 1996 inspection.

Our review of the information contained in the establishment inspection report prepared by the district office reveals violations of FDA regulations contained in Title 21, Code of Federal Regulations (21 CFR), Part 50 - Protection of Human Subjects, Part 56 - Institutional Review Boards, Part 812, Subpart D - IRB Review and Approval, and Part 814, Subpart H - Humanitarian Use Devices.

The violations were listed on the Form FDA 483, "Inspectional Observations," which was presented to and discussed with you and others at the conclusion of the inspection. The description of violations that follows is not intended to be an all-inclusive list of IRB deficiencies.

1. Failure to ensure adequate initial and continuing review of research [21 CFR 56.108, 56.110, and 814.124(a)]

The IRB reviews approximately [redacted] studies per calendar year. A primary reviewer system is often used for initial review. Generally, one member is assigned to review the protocol proposal from a medical and/or scientific standpoint and one lay member is assigned to review and make recommendations on the consent form. These reviewers present a protocol summary, recommendations, and discussion of the consent form to the full board. The IRB's procedures [redacted] do not permit the principal investigator to present the protocol summary to the full board at IRB meetings. If the primary reviewer cannot be present, a substitute primary reviewer can be designated but the substitute must have been able to thoroughly review the protocol proposal as if he or she had been the original primary reviewer. However, on [redacted] due to the absence of the primary reviewer, the principal investigator presented a summary of proposed studies [redacted] and [redacted] to the full board. On [redacted] a non-member of the IRB, with conflicting interest, was designated the primary reviewer for study [redacted] and presented the study summary to the full board.

The IRB Administrator "approved" the use of two Humanitarian Use Devices (HUDs) without presenting them to the full board for review. These include [redacted], approved as "Exempt," and [redacted], approved as "Emergency." Documentation from both sponsors specified the need for IRB approval prior to device distribution or use. The IRB Administrator was unaware of the procedures pertaining to use of these devices and did not realize these had to go before the full board. She also approved both to continue without the benefit of full board review. In addition, this administrator reviews and approves the majority of the expedited, emergency use, and exempt study submissions.

The IRB's procedures [redacted] allow continuing review to be conducted by the IRB Chair/designated member as long as the full IRB receives the information and the continuation review recommendation at the next regularly-scheduled IRB meeting. It was found that the IRB Administrator conducts most of the continuing reviews and approves studies for continuation without the opportunity for full board input and vote prior to approval. IRB members are often not aware of approvals for continuation until <u>after</u> approval letters have already been sent to investigators.

Numerous examples were observed of studies receiving approval for continuation at least a month in advance of an IRB meeting. This practice does not allow a physician/scientific member of the IRB to review adverse events and evaluate risks/benefits associated with the study. Furthermore, the information captured on the progress report form utilized by the IRB may not be comprehensive enough to permit substantive review. The IRB was informed that their current continuing review practices are unacceptable.

The criteria for IRB approval of research should be the same for continuing review as for initial review. Continuing review of a study may not be conducted through an expedited review procedure unless 1) the study was eligible for, and initially reviewed by, an expedited review procedure, or 2) the study has changed such that the only activities remaining are eligible for expedited review. Our review of studies submitted to the IRB for continuation revealed that many were not eligible for an expedited or administrative review by the IRB Administrator.

According to the IRB's procedures [redacted] continuing review is to be substantive and meaningful and include review of all study activity which has transpired during the current review period. The procedures [redacted] also require that the continuing review include "a description of any adverse events or unanticipated problems involving risks to subjects or others." It was observed that the majority of adverse event reports for the years 2001 and 2002 (seven boxes full) had not been filed by study number nor had the data been entered into the IRB's database; therefore, there is no assurance that all adverse event data was evaluated and taken into consideration during review. In one case, approval for continuation for study [redacted] was granted even though at least 10 onsite adverse events, which had not been listed on the IRB's Study Information Report (SIR) for that study, were found.

A primary reviewer is designated to review all adverse event reports. The reviewer, a retired physician, was interviewed during this inspection to explain the adverse event review process. He maintains lists of adverse events he reviews, but this review and evaluation is not documented on the adverse event report. Because of this and the fact that many adverse event reports had not been filed or entered into the database, there is no assurance that all adverse events were properly reviewed and reported to the full board. In addition, the timeframes for reporting Serious Adverse Events to the IRB are not specified in

the procedures. Therefore, the IRB may not have had access to all study activity relating to adverse events that took place during the review periods.

The IRB utilizes a [redacted] subgroup, the [redacted] to conduct full board review [redacted]. It is reportedly used in cases where a sponsor may need IRB review before the next regularly-scheduled meeting because of an emergency situation or a demonstrable need for a quick startup date. However, the [redacted] minutes of the [redacted] meeting show that numerous adverse events were presented by the primary adverse event reviewer. Also, at a [redacted] meeting, other issues discussed were HIPPA, privacy issues, database access and medical prescribing errors. It is unclear if activities of the [redacted] were shared with the regular IRB members.

Independently, this subgroup meets IRB membership requirements; however, it does not meet quorum requirements for the [redacted] member Lovelace Institute IRB. However, there is no assurance that at least five members, meeting all regulatory requirements for membership, attended all [redacted] meetings. Furthermore, without transcribed meeting minutes, it is impossible to tell if all agenda items, including adverse event reports, had actually been discussed and acted on during convened meetings.

2. Failure to prepare and maintain adequate documentation of IRB activities in accordance with 21 CFR 56.115(a)(2), (a)(5), and 812.66

IRB meeting minutes were incomplete or lacking, policies and procedures have not been updated and were incomplete, and adverse event reports had not been processed.

IRB minutes for 2001 and 2002 meetings were not transcribed. Although meeting minutes for May, June, July, and August 2002 arrived from the transcriber at the start of this inspection, minutes from the other meetings were unavailable for review. In addition, no meeting minutes covering this time frame have been reviewed and approved by the full board. A review of prior meeting agendas indicates that minutes from previous meetings are to be sent to members for review and approval; because minutes have not been available, this could not be done. Regulations require that the minutes document the following: attendance,

actions taken, vote on actions (number of members voting for, against, and abstaining), and a written summary of the discussion of controverted issues and their resolution. In addition to this information, the IRB's procedures [redacted] also require documentation of the discussion of adverse events, study reports, progress reports, and deviations from the study protocol.

The IRB minutes that were available fail to include the number of members voting for, against, and abstaining. Because the members vote "in block" it is difficult to tell the exact vote counts. During the [redacted] meeting, it was observed that the votes taken were "unanimous" even though it was unclear how many members and/or alternates had voted.

The IRB's procedures [redacted] require documentation of the IRB's rationale for significant risk/nonsignificant risk (SR/NSR) approval or disapproval decisions. However, there were no minutes available to document approval or disapproval decisions.

Records regarding each IRB member's representative capacity, indications of experience in sufficient detail to describe their anticipated contributions to IRB deliberations, and any employment or other relationship between each member and the institution are incomplete. Four of [redacted] regular members and [redacted] of three alternate members did not have CVs/resumes on file.

The IRB membership roster (updated August 2002) does not identify regular members for whom each alternate member may substitute. In addition, IRB minutes do not detail when an alternate member replaces a regular member. At the [redacted] IRB meeting, alternate members reviewed consent documents for proposed studies, even though it was unclear which regular IRB member they were replacing.

3. Failure to have and follow adequate written procedures as required by 21 CFR 56.108(a) and (b), and 56.115(a)(6)

The IRB must have and follow written procedures that describe the IRB's functions and operations. The current Institutional Review Board Policies (revised [redacted] do not meet the FDA requirements for written procedures (i.e., how the process is accomplished) in several areas. The procedures that should be added or revised include, but are not limited to, those discussed in this section.

The IRB's written policies/procedures consist of two manuals: an IRB [redacted] Some information contained in these manuals was outdated (e.g., copies of regulations, IRB membership list, study list).

There are no procedures or guidance for review and oversight of the use of Humanitarian Use Devices (HUDs) even though the IRB has approved the use of two HUDs. [The issue of the IRB's inadequate review of HUDs was discussed above under Heading 1.]

Although the procedures [redacted] indicate that the IRB will prepare and maintain adequate documentation of emergency/ compassionate use, there are no IRB procedures for reviewing emergency situations and compassionate use. The IRB Administrator reviewed and approved [redacted] (one of the above-referenced HUDs) as "Emergency," and it is unclear if emergency use procedures, as described in 21 CFR 814.124(a), were followed. She reviewed and approved study [redacted] as "Compassionate Use" without full board review. Study [redacted] was approved as a compassionate use protocol. It was scheduled for discussion at the IRB meeting scheduled for [redacted] but the meeting minutes do not reflect this study was discussed.

The IRB's continuing review procedure [redacted] which is accomplished through administrative or expedited review, is inappropriate. [See further discussion under Heading 1 above.]

The IRB procedures do not address how adverse events are handled, and timeframes for reporting Serious Adverse Events (SAEs) are not specified. Instructions to investigators for the Adverse Event Report Form state only that SAEs are to be reported to the IRB Administrator's office in a timely manner.

It is stated in the procedures that the IRB has the authority to suspend or terminate IRB approval of research [redacted] and will ensure prompt reporting of suspension or termination of IRB approval [redacted] to the IRB, appropriate institutional officials, and the appropriate governmental entity. However, the IRB failed to notify the FDA, as required [21 CFR 56.113], of two suspended studies: [redacted] was suspended for protocol violation problems, and [redacted] due to nine adverse events at the local site. In addition, there are no procedures addressing how the IRB ensures that investigators comply with FDA and IRB requirements [21 CFR 56.108].

Procedures [redacted] do not address how the IRB determines which studies require review more often than annually, as required in 21 CFR 56.108(a)(2).

The IRB [redacted] include the requirement for identification of an IDE (Investigational Device Exemption) number in the event the study is for a new investigational device. However, the IDE number for study [redacted] was not included in the application, nor was the IDE number for studies [redacted] and [redacted] prior to approval. Also, the forms provided to investigators (e.g., adverse event report, application for review) refer primarily to drug studies even though device studies are conducted at your institution.

The procedures [redacted] indicate that Lovelace Respiratory Research Institute will provide sufficient staff to support the IRB's review and recordkeeping duties. Due to the fact that minutes had not been transcribed for over 1-1/2 years and there were numerous boxes of unprocessed adverse event reports, this does not appear to be the case.

4. Failure to ensure that informed consent information meets the requirements of 21 CFR 50.20

The consent form for studies [redacted] required patients needing replacement surgery to sign a consent with the following language: "I do hereby release and forever discharge [redacted] and any related persons and entities from any and all claims arising out of the use of [redacted] . . ." Consent documents cannot contain exculpatory language that waives the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence [21 CFR 50.20].

We also noted that some violations revealed during the June 1996 inspection still had not been corrected. This included numerous deficiencies in the IRB's written procedures and in the initial and continuing review process. Documentation of IRB activities (e.g., meeting minutes, representative capacity of each IRB member, and processing of adverse events) has not been maintained. The available meeting minutes still fail to designate the number of members voting for, against, and abstaining.

Within fifteen (15) working days of receipt of this letter, please provide this office with written documentation of the specific steps you have taken or will be taking to bring your Institutional Review Board into compliance with FDA regulations. Failure to respond may result in further regulatory action, such as that described in 21 CFR 56.120 and 56.121, without further notice.

The corrective actions should include, but are not limited to, the following:

- A revision of current policies and procedures to ensure that the functions and operations of the IRB comply with all applicable federal regulations, and the timeframes within which these procedures will be developed and implemented.

- Clarification of the role and structure of the [redacted] It may be acceptable to operate as a separate IRB, with some members serving on both, as long as there is a roster for each and list of alternates who can substitute for regular members.

- Submission of IRB meeting agendas and minutes subsequent to the FDA inspection.

- Timeframe for which all data input and filing will be complete.

- How the IRB/institution has addressed the issue of insufficient IRB staff to perform all required activities.

You should direct 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 A. Crowl. A copy of this letter has been sent to FDA's Denver District Office, 6th Avenue & Kipling Street, Denver, Colorado 80225. We request that a copy of your response also be sent to that office.

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

Sincerely yours,

for Timothy A. Ulatowski
Director
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