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Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

SEP 23 1999

WARNING LETTER

Certified Mail
Return Receipt Requested

Steven C. Springmeyer, M.D.
President, Board of Directors
Virginia Mason Research Center
1000 Seneca Street
Seattle, WA 98101

Dear Dr. Springmeyer:

During an inspection that concluded on June 4, 1999, Ms. Astrida B. Mattson, an investigator with the Food and Drug Administration (FDA), inspected the Virginia Mason Research Center (VMRC) Institutional Review Board (IRB). The purpose of the inspection was to determine if the IRB's procedures for the protection of human subjects comply with FDA regulations, published in Title 21, Code of Federal Regulations, Parts 50 and 56 [21 CFR 50 and 56].

Based on information obtained during the inspection, we have determined that there were serious violations of the requirements of 21 CFR Parts 50 and 56. A copy of the list of Inspectional Observations (FDA-483) left with Dr. James Bredfeldt, the IRB Chairman, at the end of the inspection is enclosed. The deviations noted in our inspection include, but are not limited to the following:

1. **Failure to prepare detailed written procedures for conducting the review of research, including periodic review. [21 CFR 56.108(a), (b), and 56.115(a)(6)]**

At the time of inspection, the Virginia Mason Research Center Institutional Review Board Policies and Procedures dated May 20, 1999, lacked written procedures for the following:

- a. Provisions for prompt reporting to appropriate institutional officials and FDA of:
 - i. Any unanticipated problems involving risks to subjects.
 - ii. Any serious or continuous noncompliance with FDA regulations or IRB requirements.

- iii. Any suspension or termination of IRB approval.

We note that these deficiencies were corrected during the course of the inspection.

- b. Correct procedures for emergency use situations.

The emergency treatment “approval” procedures (Section VI.F.) need to be rewritten. Section VI.F., as currently written, is quoted from 21 CFR 50.23. This section of the CFR describes the exception from general requirements of informed consent, not necessarily emergency use. Emergency use is defined in 21 CFR 56.102 (d). In emergency use situations, the determination must be made as to whether the test article must be administered immediately or not. As noted in 21 CFR 56.104(c), the emergency use must be reported to the IRB within five working days. Any subsequent use of the test article at the institution is subject to IRB review. Informed consent may and should be obtained for emergency use situations whenever possible. If informed consent cannot be obtained, then full documentation of the exception must be followed as outlined in 21 CFR 50.23.

Section VI.F. currently includes the sentence, “~~_____~~”

_____ This statement incorrectly implies that existing protocols that prospectively determine use of the test article in an “emergency use” situation do not need to undergo prior full IRB review and approval.

- c. Detailed procedures for determining which studies need verification from sources other than the investigator that no material changes have occurred since the previous IRB review.
- d. Definition of “minor changes” to protocols that allow for expedited review in section VI.D.
- e. Procedures under section VI.E. that clarify that continuing review of cooperative research studies will be conducted by the full board, if continuing review of the studies does not fall into categories where expedited review is permissible.
- f. Procedures for ensuring that changes in approved research may not be initiated without IRB review and approval, except to eliminate immediate hazards to human subjects. We note that this deviation was corrected during the inspection.

2. Failure to conduct adequate continuing review of research. [21 CFR 56.109(f)]

The IRB conducts continuing review inappropriately. The current system may not adequately ensure protection of research subjects. For example:

a. All continued review is accomplished by an “expedited” process. It appears that the Chair of the IRB is the only member who reviews study files, progress reports, consent forms, amendments, and adverse event reports for continuing review. The Chair approves the studies and reports updates in the monthly agendas. There appears to be no discussion regarding the studies during convened meetings. The following are examples:

i. Study #1476 Community Oncology Program NSABP C-06 A *Clinical Trial Comparing Oral Uracil/Fluorouracil (UFT) Plus Leucovorin (LV) with 5-Fluorouracil (5-FU) Plus LV in the Treatment of Patients with Stages II and III Carcinoma of the Colon*. The study is listed in the 5/20/99 IRB meeting minutes as letter “D” under “Annuals.” A total of — subjects were randomized at Virginia Mason Medical Center (VMMC) during the year, according to the minutes. Adverse events and safety updates were also reported during the reporting period.

ii. []

b. No vote is taken to approve or disapprove studies. The following dates and numbers of studies listed for continuing review were approved without discussion or voting.

<u>Meeting Date</u>	<u>Number of Studies Due for Continuing Review</u>
2/19/98	—
3/18/99	—
4/15/99	—
5/20/99	—

c. From review of study documents and the FDA investigator’s observations during the 5/20/99 meeting of the IRB, it appears that the IRB approves all studies for a period of one year without discussion regarding the need to review more frequently than annual review.

d. The IRB approved an amended consent form on 1/10/97 used in VMRC study #8512. The form contains tests and procedures that are not part of the actual study protocol. The erroneous consent form was brought to the attention of the IRB via a subject complaint that tests and procedures described in the consent form were not being conducted. Please explain how a consent form that does not agree with the protocol was approved by the IRB.

The methods of continuing review implemented by the IRB deviate significantly from the federal regulations. The purpose of continuing review is to review the entire study, including all changes. 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. Studies that accrued subjects during the previous approved time period and were not eligible for expedited review should receive continuing review by the full board.

In conducting continuing review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (i) the number of subjects accrued; (ii) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (iii) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (iv) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB.

Continuing review should include a reexamination of the current consent form to ensure the form contains accurate, current, and adequate information regarding the study, FDA regulations, and information such as the current phone numbers and contacts for answers to research questions, subjects' rights, and the contact for research subject injuries, for example.

3. Failure to have a majority of IRB members present when reviewing proposed research at convened meetings. [21 CFR 56.108(c)]

A majority of voting members was not present at the 2/19/98 meeting where research was reviewed and approved. — of the — voting members were present. — were required for a majority. — new applications were reviewed and approved, and — studies were listed for continuing review under the "Annuals" section of the minutes. Explain how reoccurrence of such errors will be prevented.

In addition, the IRB enlisted — non-members at the 2/19/98 meeting to fulfill the IRB's quorum requirement. The non-members were not prospectively identified on the IRB membership roster as alternate members.

4. Failure to fulfill requirements for expedited review. [21 CFR 56.110]

Review of four months of meeting minutes revealed inappropriate use of expedited review procedures. The IRB Chair approves all amendments and revisions for previously approved studies and consent forms via an "expedited review" process without regard to the complexity of the amendments or revisions.

**5. Failure to accurately record the attendance and voting by IRB members.
[21 CFR 56.115(a)(2)]**

The meeting minutes for 2/19/98 list _____ as both present and absent.

The most recent list of categories of research that may be reviewed by the institutional review board through an expedited review procedure is available on the World Wide Web at <http://www.fda.gov/ohrms/dockets/98fr/110998b.txt>.

This letter is not intended to be an all-inclusive list of deficiencies that may exist with the IRB. The IRB is responsible to adhere to each requirement of the law and applicable regulations.

Based upon the demonstrated deficiencies in organizational guidelines, operational procedures, recordkeeping practices, and demonstrated deficiencies regarding continuing review, it appears that your procedures are inadequate to protect the rights and welfare of human subjects of research. Failure to make adequate corrections may result in regulatory action being initiated by the Food and Drug Administration. As described in section 56.120 of the regulations, these actions include withholding approval of new studies, direction that no new subjects be added to ongoing studies, termination of ongoing studies, and notification of State and Federal regulatory agencies.

Please notify this office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken or plan to take to bring the procedures of your Institutional Review Board into compliance with FDA requirements. If corrective action cannot be completed within 15 working days, state the time within which the corrections will be completed.

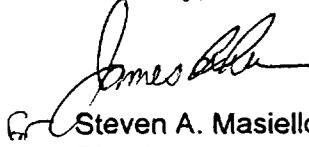
Your file will remain open until we receive your response and it is deemed adequate. The website to the *FDA Information Sheets* (<http://www.fda.gov/oc/oha/IRB/toc.html>) is provided to assist you in implementing the changes necessary to bring the IRB into compliance with applicable standards. Appendix H of the *FDA Information Sheets* provides a guide to ensure that all required elements are included in your written procedures.

Should you have any questions or comments about the contents of this letter or any aspects of the operation and responsibilities of a review board, you may contact Debra Bower, Consumer Safety Officer, Bioresearch Monitoring, Division of Inspections and Surveillance, at (301) 827-6221.

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- Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852-1448, Attention: Debra Bower, HFM-650.

Sincerely,



Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosure

Form FDA 483, Inspectional Observations, dated 5/20, 25-28 and 6/4/99

cc:

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