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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

Certified-Return Receipt Requested

WARNING LETTER

Huibert Vriesendorp, M.D.
6641 Westchester
Houston, Texas 77005

NOV 19 1996

Dear Dr. Vriesendorp:

The Food and Drug Administration (FDA) has investigated allegations that you enrolled ineligible subjects and failed to follow the protocols in studies utilizing unlicensed biological investigational new drugs, specifically _____ in violation of FDA regulations governing investigational new drugs. During the period from April 8 to 12, 1996, Mr. Joel Martinez and Mr. Bruce Taylor, investigators from the FDA Dallas District Office, and Dr. Mary Andrich, Medical Officer from the Center for Biologics Research and Review, visited M. D. Anderson Cancer Center to interview you and examine records relating to the use of the investigational antibodies.

Based on information obtained during the investigation, we believe that you have repeatedly and deliberately violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published under Title 21, Code of Federal Regulations (CFR), Parts 312, 50, and 56 (copies enclosed).

This letter provides written notice of the alleged violations and initiates an administrative proceeding to determine whether you should be disqualified from receiving investigational new drugs, as set forth under 21 CFR § 312.70.

A listing of our allegations follows. The applicable provisions of the CFR are cited for each allegation.



1. **Failure to submit an Investigational New Drug Application (IND) to FDA and failure to withhold administration of an investigational new drug until an IND is in effect. [21 CFR 312.20, 312.40(d), and 312.50]**

You administered an investigational _____ to at least one subject without filing an IND with the FDA. Our inspection determined that you administered the _____ to subject _____ in 1993. There was no IND in effect for this investigational new drug.

Contrary to your statements in your response letter dated April 21, 1996, you were not authorized by the sponsor of another IND at another institution to obtain or administer the _____. Your involvement in the study of the _____ at another institution under another sponsor's IND was terminated by that sponsor in June, 1990.

We disagree with your assessment in your response letter that documentation of this event in the subject's medical records constitutes approval to administer an investigational drug without permission of the Institutional Review Board (IRB) and FDA.

2. **Failure to fulfill the general responsibilities of investigators. [21 CFR 312.60 and Part 50]**

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of unlicensed biological investigational new drugs for the following reasons:

- A. You failed to adequately protect the safety and welfare of subjects. The IRB and the sponsor agreed upon the entry criteria in the approved protocols so that subjects would not be exposed to undue risk.
 1. You did not adhere to the eligibility criteria established in the IRB-approved protocols 92-001 and 95-004. Several subjects were administered _____ although they should have been excluded by the criteria specified in the protocol.

The following examples are illustrative, and this list is not complete:

a. Subjects _____ were enrolled _____

You provided a data sheet for subject _____ with your response letter dated April 21, 1996. The data sheet is undated, and is inadequate to refute this finding.

b. Baseline laboratory analyses were not performed for subjects _____, and

c. Subjects _____ were enrolled when _____

d. Subjects _____ were enrolled when _____ of the predicted value. Subjects _____ were enrolled when their status was poor, and subject _____ was enrolled although the _____

e. There is no evidence that you performed tests in several subjects, including subject _____ who had _____ and who underwent six cycles of investigational _____

f. Subjects _____ were enrolled although their _____

g. You reported to the sponsor (memorandum to dated March 15, 1996) that subjects "were _____ at that time and our treatment was given with full approval of the other attending physicians involved". These subjects were ineligible for inclusion in protocol 92-001.

Contrary to your response letter dated April 21, 1996, we do not consider these to be "minor eligibility issues". The M. D. Anderson Center Office of Research published their procedures for Compassionate IND in part 4 of Section VIII - Investigational drugs. The document states that the requesting physician must complete a compassionate IND Form and patient informed consent, and that these must be approved by the Chairman of the Surveillance Committee and by the office of Protocol Research. You failed to obtain a compassionate IND for the subjects listed above.

Your response letter refers to a memorandum from Dr. Zwelling dated January 8, 1996, which describes the Protocol Data Management System (PDMS) for registration of study subjects. This memorandum describes future implementation of the PDMS, and does not describe the institutional requirements during the period when protocols 92-001, 94-017, and 95-004 were open for enrollment.

2. **Subjects were administered concurrent therapies that would confound the evaluation of safety or efficacy of the investigational**
The following examples are illustrative:
 - a. Subject (enrolled in protocol 92-001), and subjects (enrolled in protocol 95-004) were administered
 - b. Subjects were administered concurrent not permitted under protocol 92-001.
 - c. Subject underwent bone marrow transplantation not permitted under protocol 95-004.
3. Subjects were administered fractionated doses of although protocol 92-001 specified that a single therapeutic dose should be administered. The fractionated doses were administered without the approval of the IRB or the sponsor.
4. You failed to perform an study with in subject By failing to perform the diagnostic imaging procedure, you proceeded to the therapy dose with which was ineffective, and exposed the subject to unnecessary a violation of section 5.4 of protocol 92-001.

5. You did not routinely test subjects for the formation of _____ to monitor for possible allergic reactions to repeated administration of _____. This requirement is stated in section 5.11 of protocol 92-001.
6. Dosimetric calculations, as specified in protocols 92-001 and 95-004, were not performed for any subjects.
7. None of the subjects enrolled in protocol 95-004 were administered the second _____ prior to the second dose of _____

The protocol states "the purpose of the second administration is to determine whether the first administration has changed normal tissue and tumor uptake of the _____

A second administration was not to be administered if the second _____ indicated an altered biodistribution due to formation of _____. The IRB should have reviewed and approved the discontinuation of the second _____ procedure because subjects would be exposed to greater risk.

8. Subject _____ received _____ labeled test article 36 days following the diagnostic dose of _____ labeled test article. Protocol 92-001 specifies that the _____ dose was to be administered from four to seven days following the _____ dose. The _____ dose was administered even though the subject's platelet value was $12,000/\text{mm}^3$, indicating that the subject had not recovered from previous procedures.
9. The _____ dose was not fractionated under protocol 95-004 for the following subjects:
10. Subject _____ received a second cycle of radiolabeled test article under protocol 95-004 even though her second _____ diagnostic scan demonstrated new areas of disease. Furthermore, the subject's record states that a CT scan was "not done within two months" at that time.

11. Therapy doses of _____ were administered under protocol 92-001 to the following subjects whose platelet counts were $\leq 50,000/\text{mm}^3$:

B. You failed to adequately protect the rights of subjects.

1. Subject _____ was administered _____ before signing the consent form for study 92-001.
2. The consent forms are broadly deficient; see item 6, below.

3. Failure to assure initial and continuing review and approval of a clinical study by an Institutional Review Board. [21 CFR 56.103(a), 312.66]

- A. You failed to report the deaths of study subjects to the IRB.
- B. You failed to notify the IRB of adverse experiences that occurred during studies 92-001 and 95-004.
- C. You administered an investigational _____ to one subject without IRB review and approval. The IRB approved protocol 92-001 which specifies that the investigational product under study is _____
- D. You failed to obtain IRB approval before you discontinued the second _____ for protocol 95-004. No subjects were managed according to the approved protocol; see item 2A(7), above.

4. Failure to maintain adequate records of disposition of the investigational drugs. [21 CFR 312.57(a) and 312.62(a)]

- A. There is no documentation of the source of the _____ administered to at least one subject.

- B. The labeling protocol and quality control analytic reports are missing for some subjects. The following examples are illustrative:
1. There are no _____ reports for subject _____ for the following dates: 2-3-94, 12-22-94, 12-28-94, and 4-20-95.
 2. There are no _____ reports for subject _____ for the following dates: 4-13-95, 8-3-95, 9-21-95, and 9-28-95.
- C. There are no prescriptions on file for some doses of investigational _____
Examples include, but are not limited to, those listed in item 4(B), above.
- D. Inventory records do not document that additional manufacturing procedures were performed, such as the filtering of the test article. There is no documentation of testing performed following such procedures to determine the activity of the product.
- E. You failed to maintain an adequate inventory of _____ including type of _____ amount, lot number, date of _____ dates and amounts of investigational _____ dispensed, and recipient identification. Drug accountability records are not adequate to identify the recipients of a particular lot of _____ investigational drug.
- F. There are no drug accountability records regarding the transfer of test article from the _____ to _____ M. D. Anderson Cancer Center. In January 1996, _____ reported to _____ that five grams of _____ were brought from _____ Your response letter of April 21, 1996, states that approximately 2.6 grams were brought from _____ Please explain the discrepancies and provide documentation supporting your response.

5. Failure to prepare and submit investigator reports. [21 CFR § 312.64]

- A. You did not promptly report to the sponsor any adverse effects that may reasonably be regarded as caused by, or probably caused by _____
For example, you did not report the reactions that occurred in subjects _____
- B. You did not submit final study reports to the sponsor as requested on several occasions since December 1995.

6. Failure to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR Part 312.60]

- A. The consent form for study 94-017 does not specify the investigational nature of the to be administered to subjects, and does not identify from which the was obtained.
- B. The consent form for study 94-017 is inaccurate and misleading in that it states "The risks of administration of is virtually negligible."
- C. The consent form for study 95-004 states "blood counts will return to pretreatment levels over time, but might require additional measures...". This statement does not accurately reflect the actual hematologic toxicity profile observed following the administration of
- D. The consent forms for protocols 92-001 and 95-004 are inaccurate and misleading in that they incorrectly report that allergic reactions were not observed during studies of at another institution. The consent forms state that allergic reactions had not been observed, and the consent form for study 94-017 states that no adverse events have been observed.
- Allergic reactions were observed at the other institution, some of which occurred during the period when you were associated with the studies at that institution. In addition, the consent forms should have been amended following the allergic reaction that was observed in subject
- E. The consent forms for studies 92-001, 94-017, and 95-004 lack a description that the subjects might experience adverse reactions related to possible development of , and that the potential for allergic reactions increases following repeated doses. The consent forms do not advise subjects that their participation could exclude them from continuing the current study or future studies involving
- F. The 'potential benefits' section of the consent form for study 95-004 contains language that is vague, coercive, and could unduly influence the prospective subjects or their legally authorized representatives.

Please submit the following information as part of a complete response to the allegations listed above:

1. Please provide a complete list of all subjects who were administered including the and whether Please identify the treatment status as "on protocol" or "off protocol".
2. Please identify all subjects who were removed from the protocol and the reason why they were "off-protocol". Please provide documentation that you notified the IRB of the change of each subject's status.
3. Please provide documentation that the sponsor and IRB approved the administration of therapeutic test article outside the restrictions of protocols 92-001 and 95-004.
4. Please provide a copy of each protocol form for each dose of administered to human subjects.
5. Please provide a copy of each prescription form for each dose of administered to human subjects.
6. Please submit copies of the dose assay slips from a dose calibrator to document the actual number of millicuries of administered to each subject who received under protocols 92-001, 94-017, and 95-004.
7. Please provide records of the specific activity of for each dose administered to human subjects.

On the basis of the above, we believe that you have repeatedly and deliberately failed to comply with the cited regulations and we propose that you be disqualified as a clinical investigator. You may reply to the above issues, including any explanation of why you should remain eligible to receive investigational drugs and not be disqualified as a clinical investigator, in a written response, or at an informal conference in my office. This procedure is provided for in section 312.70(a) of the investigational drug regulations.


Within ten (10) days of receipt of this letter, write or call me at (301) 594-2066 to indicate your intent to either request an informal conference or to respond in writing within thirty (30) days.

If you decide to request an informal conference, please be informed that a transcript of our discussions will be prepared. You may bring legal counsel with you to such a conference.

If you agree with our findings, or do not wish to avail yourself of the opportunity for an informal conference and do not wish to make a written reply to our findings, you may consider entering into a consent agreement with FDA regarding your future eligibility to receive investigational drugs. Such an agreement would terminate further administrative proceedings. If you wish to consider this option, we will forward an agreement for your review.

If we cannot come to terms on such an agreement, or if your written or oral responses to our allegations are unsatisfactory, you will be offered a regulatory hearing before the Food and Drug Administration, pursuant to Part 16 (enclosed) and section 312.70 of the regulations. This hearing will determine whether or not you will remain entitled to receive investigational new drugs. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding.

Sincerely,



for

James C. Simmons
Director
Office of Compliance
Center for Biologics Evaluation
and Research

Enclosures

- 21 CFR Part 312 (revised as of April 1, 1996)
- 21 CFR Part 16
- 21 CFR Part 50
- 21 CFR Part 56