DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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

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Warning Letter

By Certified Mail - Return Receipt Requested

CBER - 01 - 005

Steven E. Raper, M.D.
Institute for Human Gene Therapy
313A Stellar-Chance Laboratories
422 Curie Boulevard
Philadelphia, Pennsylvania 19104-4268

Dear Dr. Raper:

During an inspection conducted from November 30, 1999, to January 19, 2000, Mr. Mike Rashti, an investigator from the Food and Drug Administration (FDA) Philadelphia District Office, and Dr. Thomas Eggerman, a Medical Officer from the FDA Center for Biologics Evaluation and Research (CBER), visited the headquarters of the Institute for Human Gene Therapy at the University of Pennsylvania to examine records relating to the clinical study of an investigational adenoviral vector expressing the ornithine transcarbamylase (OTC) gene. The inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational new drugs.

Study documents show that you had a pivotal role in the conduct of the study. Although you were not responsible for all aspects of the study, you were delegated significant responsibilities. You were in a position to influence how the study was conducted. The violations listed below do not reflect all of the deficiencies in the study, but identify those for which you bear some responsibility.

Based on information obtained during the investigation, we have determined that you 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 and 50 (available at http://www.access.gpo.gov/nara/cfr/index.html). The applicable provisions of the CFR are cited for each violation listed below.

1. Failure to ensure that an investigation is conducted according to the investigational plan (protocol). [21 CFR § 312.60].

For the purpose of this letter, the version 4 revisions (dated July, 1998, and November, 1998) to sections 4.1.1 and 4.3 do not apply because the sponsor did not submit these protocol versions to FDA, and they were therefore not part of the approved investigational plan.

A. You did not follow the protocol requirement to stop the study as described in protocol Section 4.3, which states, "If a single patient develops Grade III or higher toxicity, the study will . . . be halted." Protocol Section 4.1.6 further states, "Evidence of toxicity will be measured using a modified version of the [redacted] initially developed by the [redacted] for chemotherapy trials." The table on page 3 identifies the adverse events experienced by the subjects enrolled in this study, classified in accordance with the [redacted] Based on protocol section 4.1.6, Grade III or IV toxicities are categorized as "significant," and are shown in the lightly shaded portions of the table. The unshaded portions of the table denote Grade I and II toxicities categorized as "mild" by protocol section 4.1.6. The darkly shaded portions of the table indicate that no toxicities were noted.

We acknowledge that the sponsor and FDA discussed the Grade III adverse events experienced by Subjects [redacted] and [redacted] and after each report, FDA granted permission for the sponsor to enroll an additional subject. For Subjects [redacted] and [redacted] the sponsor provided an explanation that could account for the toxicities based on the subjects' medical histories.

The following Grade III toxicities did not have an explanation, and could be related to the dose of the investigational vector.

i. You did not stop the study after Subject [redacted] developed Grade III liver enzyme elevation and Grade III anemia.

ii. You did not stop the study after Subject [redacted] developed Grade III liver enzyme elevation and Grade III hypophosphatemia.

iii. You did not stop the study after Subject [redacted] developed Grade III fever and Grade III hypophosphatemia.

iv. You did not stop the study after Subject [redacted] developed Grade III fever and Grade III hypophosphatemia.

v. You did not stop the study after Subject [redacted] developed Grade III fever.

SUBJECTS ***(Grade)***

	cohort 1	cohort 2	cohort 3	cohort 4	cohort 5	cohort 6
thrombocytopenia						
bilirubin						
transaminases (ALT or AST)						
alkaline phosphatase or 5' nucleotides						
blood ammonia						
fibrinogen	*not done*	*n.d.*			*n.d.*	*n.d.*
prothrombin time						
partial thromboplastin time						
GGT (γ-Glutamyl transpeptidase)						
Fever						
Hemoglobin						
Phosphate						

n.d. = not done

B. Subjects who failed to meet the eligibility criteria were allowed to participate in the clinical trial. Subjects were administered the investigational vector even though they should have been excluded.

i. Subject — was not eligible to participate in the study because the subject's baseline neutralizing antibody titer was 1280. Protocol version 3 states that subjects must have a titer less than 1280 to participate in the study. Subject — was infused with the test article approximately two weeks after February 23, 1998, when FDA specifically rejected the sponsor's proposal to discontinue the neutralizing antibody assessment as an entry criterion, during a telephone conversation with a representative of the Institute for Human Gene Therapy.

ii. You enrolled Subject — even though he had elevated ammonia levels of 114 micromoles on day -3, and 91 micromoles on day -1 in the immediate pre-infusion period, and thus did not meet the inclusion criterion. These measurements were the daily baseline ammonia measurements before N15 testing. Protocol versions 2, 3, and 4 (in effect after September 4, 1997) list the inclusion criteria, including the following: "F. Plasma ammonia level < 70 μM (nl 15-35 μM)." Protocol version 0 (dated April 16, 1996) and version 1 (dated November 4, 1996) state the following: "All subjects ... plasma ammonia levels must be <50 μM (nl 15-35 μM) *at the time of the study*" (emphasis added). Serum ammonia levels are critical in the screening of potential subjects. Since a subject's condition may change suddenly in OTC deficiency, the clinically most relevant levels are those measured closest to the time of vector administration.

iii. You enrolled Subject — a male, as the second patient in the sixth dose cohort. This was a violation of the agreement between the sponsor and FDA that male subjects could only be enrolled as the third subject in a dose cohort. The agreement was made during a telephone conversation between Dr. James Wilson and an FDA representative on December 13, 1996, and documented in Dr. Wilson's memorandum dated December 17, 1996, to the project team, which states, "The FDA requested to limit the number of male subjects per cohort to one and always have him be the third patient....I will incorporate these changes into the revised OTC protocol and informed consent documents as soon as possible which will be forwarded to the Penn, and CHOP IRBs as well as the RDA [FDA]."

iv. You enrolled Subject — who has a hereditary liver disease. Protocol version 1 stated that patients with a "history of hepatic or vascular disease" would be excluded from the study. You eliminated this exclusion criterion from the body of the revised protocols in versions 2, 3, and 4, but you did not identify this change on the Preface list of protocol changes forwarded to FDA and the institutional review boards (IRBs). The result of the failure to disclose this revision in the list of changes is that the revision was obscured from FDA or IRB consideration, and, therefore, the revision was not part of the approved investigational plan.

C. You did not perform protocol-required tests:

i. You did not perform the laboratory tests that the protocol required on days -3 and -1 for the subjects listed below. You cannot assure that the subjects remained eligible for the study by performing these tests weeks before the infusion of the investigational vector.

a. Subject — You performed these tests 15 and 13 days, respectively, before the infusion of the test article. There were no tests performed on days -3 or -1.

b. Subject — You performed the "day -3" tests 19 days before the infusion. There were no tests performed on days -3 or -1.

ii. You did not perform the following tests that the protocol required during the hospitalization phase of the protocol (this is not a complete list):

b. Subject — Differential count on days -3 and 7.

c. Subject — Differential count on days 2, 4, 6 and 9. ALT and AST on day 8. CBC on days 6 and 9.

d. Subject — Baseline CBC and differential count at day -3; previous correspondence from the sponsor explained that the sample was not properly labeled and, therefore, was not analyzed. A pre-infusion CBC should have been performed on days -2 or -1. On the day of the infusion, lab testing revealed an abnormal red cell count, hemoglobin (Grade II), and hematocrit. Pre-infusion testing would have revealed abnormalities that should have resulted in delay of the

vector infusion. This subject subsequently developed a Grade III hemoglobin depression and other abnormalities that continued to study day 150.

e. Subject — There was no laboratory testing (creatinine, BUN, PA/PTT, CBC, and platelet count) on pre-infusion day -3.

iii. You did not perform the following tests that the protocol required during the post-hospitalization follow-up phase of the protocol (this is not a complete list):

a. Subject — Platelet count on day 60.

b. Subject — Creatinine and BUN on day 68.

c. Subject — Creatinine and BUN on days 61 and 152. Platelet count on day 152.

d. Subject — All required laboratory tests (liver function tests, CBC, and differential count) on days 60 and 150.

e. Subject Gamma glutamyl transpeptidase (GGT) on days 15, 28, 60, and 150. Subject — was discharged from the University of Pennsylvania Hospital with a Grade III GGT elevation. You did not ensure that this subject was retested on days 15, 28, 60, and 150 to determine if or when the value returned to normal. Although the participating laboratory did not routinely include GGT as part of its standard panel of liver function tests, you should have specifically requested the extra test.

D. During a telephone conversation on February 23, 1998, an FDA representative instructed Mr. Phil Cross, representative of the Institute for Human Gene Therapy, to allow at least 30 days, or more if necessary, between infusion of subjects to determine whether any anemia resolved before you infused an additional subject. This conversation is documented in the notes of the study team meeting held on February 25, 1998. On March 9, 1998, Subject — was infused with the investigational vector, fourteen days after the infusion of Subject —

2. **You failed to promptly report to the Institutional Review Board unanticipated problems regarding the safety of the study. [21 CFR 312.66].**

A. You failed to notify the IRB of adverse events according to the provisions of the protocol sections 4.3., which states, "If two patients develop mild (Grade II) toxicity, the study will be put on clinical hold until an explanation acceptable to us, the CHOP IRB, the Penn IRB, and the FDA is achieved. If a single patient develops Grade III or higher toxicity, the study will also be halted."

You failed to report the toxicities listed below to the Children's Hospital of Philadelphia IRB and the University of Pennsylvania IRB as required by the protocol.

i. Grade II toxicities in dose cohort two -- Subjects [redacted]

ii. Grade II toxicities in dose cohort three -- Subjects [redacted]

iii. Grade III toxicities in dose cohort four -- Subjects [redacted], and 014.

iv. Grade III toxicities in dose cohort five -- Subjects [redacted]

v. Grade III toxicity in dose cohort six — Subject [redacted]

B. You failed to report to the University of Pennsylvania IRB and the Children's Hospital of Philadelphia IRB that FDA required that you add an additional subject to the fourth dose cohort following the Grade III adverse event experienced by Subject [redacted]

3. **You failed to promptly report changes in the research activity to the Institutional Review Board and made changes in the research without IRB approval. [21 CFR 312.66].**

You submitted protocol amendment version 4 (dated November 1, 1998) to the University of Pennsylvania IRB and to the Children's Hospital of Philadelphia IRB with a cover letter dated January 11, 1999. The Preface of the Protocol purports to identify all modifications during the course of the study. However, the Preface omitted several protocol changes. The body of the revised protocol identified some of the revisions, but the changes were not identified in the purportedly complete Preface list of protocol changes. Dozens of protocol changes were identified in the Preface list, yet the following important changes were omitted. The following items reflect significant changes in the design of the protocol that were omitted from your list of changes:

A. The "Preface" states that this protocol version lists "... modifications by the Investigators after the enrollment of the ***third*** cohort" (emphasis added). This information is misleading and inaccurate because as of January 11, 1999, you had enrolled four subjects (Subjects [redacted] in the fourth dose cohort, and all had experienced Grade III adverse events.

B. You failed to include in the Preface list of modifications the significant discontinuance of the Grade III/IV stopping rules that were in effect through Subject [redacted]

C. You omitted from the Preface list of modifications the significant changes to Section 4.1.1 "Research Design and Methods" in protocol version 4. The effects of these revisions include the following: (1) it became conditional rather than mandatory to add an additional subject to the dose cohort if one subject develops a mild toxicity (Grade I-II); (2) you eliminated the provision to put the study on hold if two subjects develop mild toxicity; (3) you eliminated the Grade III-IV stopping rule; and, (4) you removed the provision to stop the study if three subjects in a dose cohort developed high titer neutralizing antibodies. These protocol revisions reflect significant changes that affect the safety of study subjects.

D. You omitted from the Preface list of modifications the significant changes to Section 4.3 "Completion/Termination of Study and Safety Monitoring" in protocol version 4. The effects of these revisions include the following: (1) it became conditional rather than mandatory to add an additional subject to the dose cohort if one subject develops a mild toxicity (Grade I-II); (2) you eliminated the provision to put the study on hold if two subjects develop mild toxicity; (3) you eliminated the requirement to halt the study if Grade III or higher toxicity occurs; and, (4) you eliminated the requirement that the IRBs and FDA participate in the decision as to whether it is appropriate for the study to resume after a mild (Grade II) adverse event in two subjects. These protocol revisions reflect significant changes that affect the safety of study subjects.

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

A. You did not amend the informed consent document following the Grade III liver enzyme elevations experienced by Subjects [redacted] In a letter to FDA dated January 13, 1999, signed by you on behalf of the study sponsor, you stated your "intention not to enroll patients with a history of previous intravenous drug administration...[and]...patients who are treated chronically with Dilantin and/or Lamictal...." After you recognized the increased level of risk these conditions presented, you should have

amended the informed consent document to inform potential subjects that these conditions could expose them to unacceptable risks if they participated in the study.

B. You did not amend the informed consent document following the Grade III liver enzyme elevations experienced by each of the four subjects enrolled in the fourth dose cohort (Subjects [redacted]. These were "significant" adverse events as defined in protocol section 4.1.6. Nevertheless, despite this important evidence of increased risk, you failed to provide potential subjects contacted after the fourth dose cohort with information about this possible risk of participation.

C. You did not use the IRB-approved consent form to obtain the consent to perform DNA testing from Subject [redacted] who was infused on June 6, 1998. The subject signed a consent form other than the IRB approved consent form on November 11, 1999.

D. You did not amend the informed consent document to inform potential subjects that (1) higher doses of vector were associated with disseminated intravascular coagulation (DIC) in animals, and (2) that the infusion of the viral vector might result in DIC for the human study subjects. Monkey AH4T was infused with the investigational vector in study #98-63 on October 27, 1998. Within two days the monkey developed symptoms of DIC. Two other monkeys that received different, but related vectors, were euthanized within five days of vector infusion due to severe DIC. Yet, you failed to amend the informed consent document to inform prospective subjects of the possibility of this potentially life-threatening adverse event, and you proceeded to infuse Subject [redacted] on November 17, 1998, and Subject [redacted] approximately four months later, without amending the consent form and obtaining approval by the IRBs.

E. You did not amend the informed consent document to include the discomforts experienced by the subjects enrolled in the study. Significant periods of chills, nausea, and vomiting were experienced by most subjects, yet you did not inform prospective subjects that these symptoms were likely to occur. Prospective subjects for the later dose cohorts might not have agreed to participate in the study if they had known that these symptoms were expected to occur. In addition, as the study progressed, subjects were routinely administered other medications in addition to acetaminophen to try to prevent the development of high fevers. The consent form states only that Tylenol would be administered.

5. Failure to maintain adequate case histories of individuals treated with investigational drugs. [21 CFR 312.62(b)].

A. You failed to maintain source laboratory records to verify that the [redacted] testing was performed during the screening of Subject [redacted]

B. You failed to maintain source laboratory records to verify that a serum ammonia screening test was performed for Subject [redacted]

C. At the time of the inspection, you failed to include the results of the following testing in the subject's case history:

TEST	Day 14	Day 28	Day 60	Day 150
Differential count	Subjects [redacted]	Subjects [redacted]	Subjects [redacted]	Subjects [redacted]
Liver function test	[redacted]	[redacted]	[redacted]	[redacted]
CBC	[redacted]	[redacted]	[redacted]	[redacted]

FDA acknowledges that following the inspection, most of these missing test results were subsequently retrieved from the laboratories where the testing was conducted. However, you should have incorporated these results in the subjects' medical histories shortly after they were performed, so that the condition of each subject could be assessed.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of investigational drugs. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

Please notify us, in writing, within fifteen (15) business days after receipt of this letter, of the steps you have taken or will take to correct these violations and to prevent the recurrence of similar violations in future studies. If corrective actions cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. This letter does not preclude the possibility of a corollary judicial proceeding or administrative action concerning these violations.

Failure to achieve correction may result in enforcement action without further notice. The actions could include initiation of disqualification proceedings, which may render a clinical investigator ineligible to receive investigational new drugs.

Please send your written response to:

Patricia Holobaugh (HFM-664)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 29852-1448
Telephone: (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's Philadelphia District Office, U.S. Customhouse, 2nd and Chestnut Streets, Room 900, Philadelphia, PA 19106.

Sincerely,

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

cc: Children's Hospital of Philadelphia IRB
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Philadelphia, Pennsylvania 19104

Committee on Studies Involving Human Beings
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