DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

12

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

Notice of Initiation of Disqualification Proceeding and Opportunity to Explain

NOV 30 2000

By Certified Mail - Return Receipt Requested

James M. Wilson, M.D., Ph.D.
Institute for Human Gene Therapy
University of Pennsylvania Health System
204 Wistar Institute
3601 Spruce Street
Philadelphia Pennsylvania 19104-4268

Dear Dr. Wilson:

The Food and Drug Administration (FDA) has investigated allegations that you failed to fulfill the responsibilities of a clinical investigator for a study utilizing an unlicensed biological investigational new drug, an adenoviral vector, in violation of FDA regulations governing investigational new drugs. During the period 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 (IHGT) to inspect the records relating to the use of the investigational adenoviral vectors. This inspection was conducted as part of FDA's Bioresearch Monitoring Program which includes inspections designed to review the conduct of research involving investigational articles.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or 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. These regulations are available at http://www.access.gpo.gov/nara/cfr/index.html.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational articles as set forth under 21 CFR § 312.70.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. 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. On June 21, 1997, you signed the FDA Form 1572, Statement of Investigator, in which you agreed to conduct the study in accordance with the protocol and applicable regulations. You identified that several subinvestigators would assist you in the conduct of the study, but as the clinical investigator you were responsible for all aspects of the study.

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

A. You failed to adequately protect the safety and welfare of subjects.

i. You failed to abide by the safety provisions required in the protocol; see item 2.A., below.

ii. You enrolled subjects who were not eligible for the study; see item 2.B., below.

iii. You failed to obtain proper IRB approval of protocol modifications; see item 4, below.

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

i. The consent form section titled, "We are doing a number of things to reduce these risks" states, "We also will ***discuss*** *[emphasis added]* the results of testing of each group of patients within a single dose level with the Food and Drug Administration before proceeding to the next dosage group." Although IHGT submitted a report about the Grade III adverse events that occurred for each of the four subjects in dose cohort four, IHGT representatives did not have a conversation with FDA or obtain verbal permission to proceed to the next dose level, as had occurred for each previous dose escalation. Therefore, prospective subjects for dose cohort five were misled as to FDA's active involvement in the decision to proceed to these dose levels.

ii. Additional items are in item 5, below.

2. 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, in your role as sponsor, you 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 ——— initially developed by the ——— for chemotherapy trials." The table on page 4 identifies the adverse events experienced by the subjects enrolled in this study, classified in accordance with the ——— 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, in your role as sponsor, you discussed the Grade III adverse events experienced by Subjects ——— with FDA, and after each report FDA granted you permission to enroll an additional subject. For Subjects ——— you 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 — developed Grade III liver enzyme elevation and Grade III anemia.

ii. You did not stop the study after Subject —developed Grade III liver enzyme elevation. Subject — also had Grade III hypophosphatemia.

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

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

v. You did not stop the study after Subject — 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	*n.d.*	*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 your 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. The telephone conversation was documented in notes of a meeting you attended.

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 FDA and you, in your role as sponsor, that male subjects could only be enrolled as the third subject in a dose cohort. The agreement was made during a telephone conversation between you and an FDA representative on December 13, 1996, and documented in your 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 protocol-required tests during the hospitalization phase of the protocol (this is not a complete list):

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

b. Subject — Differential count on day 4.

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 — CBC and differential count on day 9.

e. Subject — Differential count on day 4.

f. Subject — Differential count on day 2 and at discharge.

g. Subject — Differential count on days 2 and 6.

h. 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.

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

j. Subject — No differential count on day 6.

k. Subject — No differential count on day 2.

l. Subject — No differential count on day 6 and at discharge.

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 the infusion of an additional subject. This conversation is documented in the notes of the study team meeting, which you attended, held on February 25, 1998. On March 9, 1998, Subject — was infused with the investigational vector, fourteen days after the infusion of Subject —

3. You failed to assure that the Institutional Review Board would be responsible for the initial and continuing review of the clinical study by failing to submit accurate reports regarding the safety of the study. [21 CFR 312.66].

A. On August 11, 1997, you submitted a progress report and request for reapproval to the University of Pennsylvania IRB which contained significant inaccuracies.

i. You state in the cover letter that the first subject developed a mild anemia that was most likely related to the amount of blood drawn for testing. You further state that the amount of blood was decreased by about half for the subsequent subjects, and that "using this approach the following two participants did not develop anemia." This statement is incorrect because Subjects — and — also developed Grade I anemia.

ii. The form entitled, "Report for Reapproval of Research Involving Human Beings" reported the progress of the first three subjects who were administered the investigational vector. You answered the question "Total number of subjects experiencing adverse effects" as "0." You did not report the Grade I and Grade II reactions experienced by each of the three subjects enrolled to date.

B. You submitted misleading and inaccurate statements in the annual report and request for reapproval dated August 14, 1998, to the University of Pennsylvania IRB. You submitted a letter containing some of the same language to the Children's Hospital of Philadelphia IRB in a letter dated June 29, 1997 [sic; we presume the correct date is June 29, 1998]. The annual report and request for reapproval reported the safety of the first ten subjects (Subjects ————) who were administered the investigational vector.

i. Your letter states, "there have been no significant treatment-related or procedure-related toxicities...." This statement is misleading and inaccurate because you failed to disclose the Grade III elevation in transaminases experienced by Subject — an adverse event which occurred two months before the date of your progress report.

ii. Your letter states, "within 6 days of the vector infusion, 55.5% of the study participants have had elevations in their transaminases, less than 1.5 times the upper limit of normal." This statement is misleading because it implies that the only transaminase elevations are within this range. The following table identifies the transaminase values greater than 1.5 times the upper limit of normal (ULN) that dispute your statement.

subject	ALT - times upper limit of normal	AST - times upper limit of normal
—		**2.0 - Grade I**
—		**1.6 - Grade I**
—	**3.7** (day 8) **- Grade II**	**3.4** (day 7) **- Grade II**
—	**1.7 - Grade I**	**1.7 - Grade I**
—	**5.5 - Grade III**	**7.9 - Grade III**

In addition, this statement is misleading because you did not report two elevated transaminase values that occurred on study days seven and eight.

iii. You submitted a table of adverse events ("as of 07/98") for Subjects — through — That table reports selected adverse events for the 48 hour period after infusion of the test article. By reporting only the adverse events that occurred during the initial 48 hour period, you did not accurately report the adverse events that occurred after 48 hours, including the following: (1) By day 4 after the infusion, Subject — developed Grade III elevated ALT, not Grade II as you report; (2) Subject — developed Grade I anemia, but the table reports "*to be determine*" [sic] even though the subject was discharged before this table was submitted to the IRB; and, (3) the table does not report the other adverse events identified in protocol Table 4 (see the table on page 4 of this letter).

C. You submitted misleading and inaccurate information in the annual report and request for reapproval dated August 9, 1999, to the University of Pennsylvania IRB. The annual report and request for reapproval reported the safety of Subjects — through — who were administered the investigational vector.

i. The cover letter states, "No serious adverse effects have occurred as a result of this study. There have been no significant treatment-related toxicities or procedure related toxicities, and all participants have remained well." This information is false and misleading because you did not report the Grade III toxicities, as defined section 4.1.1 in the protocol, experienced by Subjects —through — since the previous report a year earlier. The annual report, therefore, misrepresented the true nature of the toxicities experienced by these six subjects.

ii. The table of adverse events attached to Appendix B to your August 9, 1999, annual report and request for reapproval does not accurately report the following toxicities:

Subject	Parameter	Grade reported to IRB	Actual Grade
—	AST elevation	Grade 2	Grade 3
—	Platelets	--	Grade I
—	Anemia	--	Grade 1
—	Fever	Grade 2	Grade 3
—	Fever	Grade 2	Grade 3

D. You failed to notify the IRB of adverse events according to the provisions of the protocol sections 4.3. Section 4.3 of the protocol 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."

In addition, you failed to report the following toxicities 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].

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

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

E. 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]

4. You failed to accurately and completely identify changes to the research activity for Institutional Review Board review and evaluation. [21 CFR 312.66].

A. You changed two entry criteria identified in protocol version 1 without IRB approval. You submitted protocol version 2 to the University of Pennsylvania IRB on August 11, 1997. The cover letter states the following: "At the completion of this first participant cohort, we are submitting for your review Protocol Version 2.0 that contains many modifications. The Preface of the Protocol lists all modifications, but several modifications are also highlighted [in the cover letter] below." You did not identify these changes on the Preface of the Protocol that you represent as listing all changes. You listed dozens of protocol changes in the Preface, including other changes in the listing of inclusion and exclusion criteria in the Preface section entitled "Participant Criteria." Yet, the following important changes were excluded:

i. You changed the inclusion criterion of serum ammonia from less than 50 micromoles (protocol version 1) to less than 70 micromoles (in all later versions). The revised criterion was only identified on protocol page 19 in section 3.2.2.

ii. You eliminated the exclusion criterion of "history of hepatic or vascular disease" (protocol version 1) from all later versions. If this criterion had remained in the protocol, then Subject [redacted] should have been excluded from the study based on a hereditary dysbilirubinemia.

B. You misled the IRB regarding the performance of cytotoxic lymphocyte (CTL) assays as part of the study. All versions of the protocol describe that you would "obtain blood for immunology tests such as CTL" at baseline and at several time points during the hospitalization and follow-up phases of the study. Thus, you assured reviewers that the results of the CTL assays would be used to (1) assess potential subjects for high CTL activity to evaluate baseline immunity and, therefore, eligibility; and (2) measure the development of an immune response to the viral vector that could potentially impact the safety of study subjects. In fact, as of the time the study was halted, and as late as April 6, 2000, the CTL assay had not been fully developed or standardized, and subjects' samples had not been assayed.

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

A. You failed to revise the informed consent document when requested to do so by FDA. In FDA's letter dated June 13, 1996, sent to you in your role as sponsor of the research, FDA requested that you add additional information to the informed consent document, including an instruction that subjects were not to donate blood or gametes, and a description of the potential germ-line effects of gene therapy. You expressly confirmed in writing, in your letter dated October 7, 1996, that you added the information not to donate blood or gametes to the consent form. In fact, you did not add such wording to the consent form submitted to the IRBs at any time during the study. This information was important to adequately inform the potential study subjects whose consent was sought.

B. You did not amend the informed consent document following the Grade III liver enzyme elevations experienced by Subjects [redacted] In your letter to FDA dated January 13, 1999, 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.

C. 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.

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 Subjec — on November 17, 1998, and Subject — 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 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.

6. 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 — testing was performed during the screening of Subject —

B. You failed to maintain source laboratory records to verify that serum ammonia screening tests were performed for Subject —

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 —	Subjects ' —	Subjects —	Subjects —
Liver function test	[			]
CBC	↓			

FDA acknowledges that following the inspection, most of these missing tests 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 studies of investigational adenoviral vector products.

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations, and it proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an 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 by regulation 21 CFR 312.70(a).

Within fifteen (15) days of receipt of this letter, write me to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to Mr. Steven A. Masiello, Office of Compliance and Biologics Quality, HFM-600, Food and Drug Administration, 1401 Rockville Pike, Rockville, Maryland 20852-1448.

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and you may be accompanied by a representative. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered the opportunity to request a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (available at the Internet address identified on page 1 of this letter) and 21 CFR 312.70. Such a hearing will determine whether or not you will remain entitled to receive investigational products. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely,

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

Enclosure
Proposed consent agreement