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

By Certified Mail – Return Receipt Requested

FEB - 8 2002

Notice of Opportunity for Hearing

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 information indicating that you repeatedly and deliberately violated federal regulations in your capacity as investigator in clinical trials with unlicensed biological and investigational new drugs, specifically, an adenoviral vector. These violations provide the basis for the withdrawal of your eligibility as a clinical investigator to receive investigational new drugs.

By letter dated November 30, 2000, the Center for Biologics Evaluation and Research (CBER) provided notice of the matters complained of and offered you an opportunity to respond to them in writing or at an informal conference pursuant to § 312.70(a) of Title 21 of the Code of Federal Regulations (CFR). The letter also gave you the option of entering into a consent agreement with the agency, thereby terminating any administrative proceeding. You chose to respond in writing, in your letter dated March 8, 2001 (March 8th letter). CBER has concluded that your written explanations fail to adequately address the violations as set forth below. Accordingly, you are being offered an opportunity for a regulatory hearing pursuant to 21 CFR Part 16, on the question of whether you are entitled to receive investigational new drugs.

The allegations involve the following clinical study in which you participated: "Recombinant Adenovirus Gene Transfer in Adults with Partial Ornithine Transcarbamylase Deficiency (OTCD)."

A listing of specific violations follows. 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 Form FDA 1572, Statement of Investigator, in which you agreed to conduct the study in accordance with the investigational plan and applicable regulations. You stated 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.

Your March 8th letter describes your role in the study as that of the "sponsor of the trial with responsibility for oversight of compliance with the protocol." You also were the investigator of the study, as evidenced by your signed Form FDA 1572, and your actions during the conduct of the study. While you assert that you delegated many aspects of subject recruitment and subject management to others, you were the responsible leader of the investigational team. Indeed, you were present when prospective subjects' cases were discussed, and when protocol modifications were considered at the OTCD team meetings.

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

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

i. You failed to abide by the safety provisions required in the protocol. Section 4.3 states, "If a single patient develops Grade III or higher toxicity, the study will . . . be halted." You did not follow this requirement to stop the study after subjects developed the following Grade III toxicities which were expressly identified as stopping criteria in Table 4 of the protocol.

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

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

ii. You enrolled subjects who were not eligible for the study because they had conditions that suggested they were at greater risk. Subjects were administered the investigational vector even though they should have been excluded from the study according to the requirements you established in the protocol.

a. Subject [redacted] 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 baseline neutralizing antibody titer less than 1280 to participate in the study. During a February 23, 1998 telephone conversation between an IHGT representative and FDA, FDA specifically rejected your proposal to remove this requirement from the protocol and discontinue the neutralizing antibody assessment as an entry criterion. Approximately two weeks later, Subject [redacted] was infused with the test article, even though the subject's baseline neutralizing antibody titer was not less than 1280.

In your March 8th letter you acknowledge that there should have been no confusion about the meaning of the term "less than" 1280.

b. You enrolled Subject [redacted] 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 version 3[1] states that "Plasma ammonia level < 70 µM (nl 15-35 µM)" are required for inclusion in the study. 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.

c. You enrolled Subject [redacted] a male, as the second patient in the sixth dose cohort. This was a violation of the verbal agreement between FDA and you that male subjects (whose condition may be more fragile than female 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

[1]For the purpose of this letter, the version 4 revisions (dated July, 1998, and November, 1998) to sections 4.1.1 and 4.3 of the protocol 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.

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]."

B. You failed to adequately protect the rights of subjects because you failed to obtain informed consent, as described in item 5, below.

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

A. You failed to abide by the stopping criteria contained in the investigational plan, as described in item 1.A.i, above.

B. You enrolled ineligible subjects and administered the investigational vector to ineligible subjects, as described in item 1.A.ii, above.

C. You did not perform protocol-required tests:

i. You did not perform the pre-study ammonia tests required by the protocol on days -3 and -1 for the subjects listed below.

a. Subject [redacted] You performed the only pre-study ammonia tests 15 and 13 days before the infusion of the test article. There were no ammonia tests performed on days -3 or -1.

b. Subject [redacted] You performed the only pre-study ammonia testing 19 days before the infusion. There were no ammonia 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 [redacted]. Differential count (to determine the proportion of white blood cell populations) on days 2, 4, 6 and 9. Liver enzymes SGPT (serum glutamic pyruvic transaminase, or ALT) and SGOT (serum glutamic oxaloacetic transaminase, or AST) on day 8. Complete blood count (CBC) on days 6 and 9.

b. Subject [redacted] Baseline CBC and differential count at day -3. 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.

iii. You did not perform tests that the protocol required during the post-hospitalization follow-up phase of the protocol. For example, no required laboratory tests (liver function tests, CBC, and differential count) were performed on days 60 and 150 for Subject [redacted], apparently because the subject failed to appear for follow-up tests. According to the memorandum addressed to you dated June 5, 1998 (attachment F to your March 8th letter), before infusion of the investigational vector, your staff reported concerns that this subject might not complete the later follow-up visits.

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 Institutional Review Board (IRB) which contained significant inaccuracies.

i. You stated in the accompanying 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 stated 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 [redacted] and [redacted] 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 first three subjects.

Your March 8th letter states that corrected information was submitted to the University of Pennsylvania IRB in subsequent annual reports dated August 14, 1998, and August 9, 1999. However, submission of accurate information for subjects [redacted]

through [redacted] one year later prevented the IRB from conducting a full, continuing review of the risks to subjects and issues related to dose escalation and frequency of IRB review.

Moreover, even if the data were corrected one year later, your cover letter to that corrected report stated, "there have been no significant treatment-related toxicity or procedure-related toxicities...."

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 [redacted] who were administered the investigational vector.

i. Your June 29th and August 14th letters state, "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 [redacted] an adverse event which occurred on June 25, 1998.

ii. Your August 14th 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 highest transaminase elevations were within this range. The following table identifies the transaminase values greater than 1.5 times the upper limit of normal (ULN) that you failed to disclose.

subject	ALT - times upper limit of normal	AST - times upper limit of normal
[redacted]	[illegible]	**2.0 - Grade I**
[redacted]	[illegible]	**1.6 - Grade I**
[redacted]	**1.7 - Grade I**	**1.7 - Grade I**
[redacted]	**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.

subject	ALT - times upper limit of normal	AST - times upper limit of normal
[redacted]	**3.7** (day 8) - **Grade II**	**3.4** (day 7) - **Grade II**

iii. You submitted a table of adverse events ("as of 07/98") for Subjects [redacted] through [redacted] 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 [redacted] developed Grade III elevated ALT, not Grade II as you report; (2) You failed to report that Subject [redacted] developed Grade I anemia because your table reports that the hemoglobin result is *"to be determine"* [sic] even though the hemoglobin test results showing the anemia were available and the subject was discharged before this table was submitted to the IRB; and, (3) the table does not report other adverse events according to the selected criteria in protocol Table 4.

Your March 8th letter states that the correct information was submitted to the University of Pennsylvania IRB in the annual report dated August 9, 1999. Submission of accurate (corrected) data one year late did not alter the fact that the IRB was forced to depend on the misleading submission during the previous year, when it considered whether subsequent dose escalation should be discontinued or whether more frequent continuing review should be required.

Moreover, even if the data were corrected inside the August 9, 1999 report, your cover letter to that report still misleadingly stated, "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."

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 [redacted] through [redacted] 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 in section 4.1.1 in the protocol, experienced by Subjects [redacted] through [redacted] 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
[redacted]	AST elevation	Grade 2	Grade 3
[redacted]	Platelets	--	Grade I
[redacted]	Anemia	--	Grade 1
[redacted]	Fever	Grade 2	Grade 3

Your March 8th letter explains that this was the last annual report to the IRB. The study was terminated in September, 1999.

D. You failed to notify the IRBs 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. [Emphasis added.] If a single patient develops Grade III or higher toxicity, the study will also be halted." You failed to report the following toxicities selected for inclusion in Table 4 of the protocol 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 [redacted]

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

v. Grade III toxicity in dose cohort six — 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 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 modifications on the Preface of the Protocol that you represent as listing all changes, and you did not highlight them in the cover letter. You listed dozens of protocol modifications 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 failed to report to the University of Pennsylvania IRB and the Children's Hospital of Philadelphia IRB a change in the investigational plan related to the safety of the study. FDA required you to add an additional subject to the fourth dose cohort following the Grade III adverse event experienced by Subject [redacted]

C. You misled the IRB regarding the performance of cytotoxic lymphocyte (CTL) assays as part of the study. All versions of the protocol state 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.

Your March 8th letter claims that under the protocol, CTL assays were optional. You contend that the term "...**such as**..." (emphasis added) allowed the tests to be optional, and that the CTL assay results were not required to establish eligibility for enrollment. On the contrary, protocol versions 3 (November, 1997) and 4 (November, 1998) state the following in section 4.1.6: "Blood to test for CTL, proliferation assays, and neutralizing antibodies **will be obtained at day -56**..."[emphasis added]. The CTL was not an optional test.

According to your response, you were unable to perform the CTL tests due to funding and staffing limitations. You provided no explanation why this element of the protocol was not removed before version 4 was submitted to the IRB if, as you claim, you were not able to conduct the assay.

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

A. You failed to inform subjects that they should not donate blood or gametes, and you failed to inform subjects that gene transfer had potential to alter the genetic composition of reproductive cells. In FDA's letter dated June 13, 1996, sent to you in your role as sponsor of the research, FDA requested that additional information be added 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 had added the instruction 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, and you did not describe the potential effects of gene transfer on reproductive cells. This information was important to adequately inform the potential study subjects whose consent was sought.

Your March 8th letter acknowledges that the informed consent documents should have been amended to include this information.

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.

Your March 8th letter acknowledges that the informed consent documents should have been amended to include this information.

C. 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.

Your March 8th letter acknowledges that the informed consent documents should have been amended to include this information.

D. You did not amend the informed consent document to include information about 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.

Your March 8th letter acknowledges that the informed consent documents should have been amended to include this information.

Pursuant to 21 CFR §§ 16.22 and 312.70(a), you are hereby notified of your opportunity for a regulatory hearing before FDA to determine whether you should be disqualified from receiving investigational drugs. The matters to be considered at the hearing are set forth in paragraphs 1 through 5, above. Under FDA regulations, you have the right to be advised and represented by counsel at all times. Any regulatory hearing on this matter will be governed by the regulations in Title 21 of the Code of Federal Regulations, Part 16, and the FDA's guidelines on electronic media coverage of public administrative proceedings, 21 CFR § 10, Subpart C. Copies of those regulations are available at http://www.access.gpo.gov/nara/cfr/index.html.

Your written request for a hearing must be postmarked, if mailed, or received, if faxed (with the original to follow by mail), within ten (10) working days of receipt of this letter. Please address the letter to:

Dr. James F. McCormack, Coordinator
Bioresearch Monitoring Program
Division of Compliance Policy (HFC-230)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
Telephone (301) 827-0425
Facsimile (301) 827-0482

If no response to this letter is received by that time, you will be deemed to have waived your right to a regulatory hearing, and a decision in this matter will be made based on the facts available to the agency.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that warrants a hearing. Pursuant to 21 CFR § 16.26, a request for a hearing may be denied, in whole or in part, if the Commissioner or his delegate determines that no genuine and substantial issue of fact has been raised by the material submitted. A hearing will not be granted on issues of policy or law. Written notice of a determination of summary judgment will be provided, explaining the reasons for denial of the hearing.

If you wish to respond but do not desire a hearing, you should contact Dr. McCormack within the time period specified above and send a written response containing your reply. The letter should state that you waive your right to a hearing and that you want a decision on the matter to be based on your written response and other information available to the agency.

The agency's offer to enter into a consent agreement remains open. Entering into a consent agreement would terminate the administrative procedures, but would not preclude the possibility of a corollary judicial proceeding. You were sent a draft consent agreement enclosed with FDA's letter to you dated November 30, 2000. If you would like to choose this option, please contact Dr. McCormack.

No final decision by FDA has been made at this time on your eligibility to continue to use investigational drugs. Moreover, there will be no prejudgment of this matter if you decline to enter into a consent agreement and decide instead either to request a regulatory hearing or to request that the decision be based on information currently available to the agency.

Please inform Dr. McCormack within ten (10) working days whether you wish to request a hearing or to have this matter resolved by consent agreement or based on the information available to the agency.

Sincerely yours,

Dennis E. Baker
Associate Commissioner for
Regulatory Affairs

Enclosures
21 CFR Part 10, Subpart C
21 CFR Part 16
21 CFR Part 312