



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

M38971

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

By Certified Mail - Return Receipt Requested

CBER - 00 - 026

Warning Letter

JUL 3 2000

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

Dear Dr. Wilson:

During an inspection conducted from February 14 to March 1, 2000, Mr. Anthony Charity, an investigator from the Food and Drug Administration (FDA) Philadelphia District Office, and Dr. Anne Pilaro, a Toxicologist from the FDA Center for Biologics Evaluation and Research (CBER), inspected the nonclinical laboratory facility in the Institute for Human Gene Therapy (IHGT). The purpose of the inspection was to determine whether your facility's activities and procedures comply with applicable FDA regulations. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research involving investigational new drugs.

The inspection focused on the general operations of the laboratory and the general conduct (not a complete audit) of the following three studies of investigational virus vectors: (1) 98-33 — C

⇒ (2) 98-54 — C
and, (3) 98-63 — "Evaluation of Toxicity of H5.000CMVhOTC, H5.001CBhOTC, and H5.110CBhOTC Vectors in the Liver of Non-human Primates."

FDA has reviewed your firm's letter dated May 4, 2000, in which you responded to the Form FDA 483 - List of Inspectional Observations discussed with and issued to you at the end of the inspection. Your firm's response purports to explain the source of some of the deviations and proposes corrective actions. For some deviations, your response states that your firm has documents that would refute FDA's findings, but your response failed to include copies of these documents. Our comments regarding your explanations will be addressed below. Statements designated with "→→" indicate that we request additional information.

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Based on the information obtained during the inspection, we conclude that you have failed to fulfill the obligations of a sponsor of nonclinical studies with investigational vectors, and violated Good Laboratory Practice (GLP) regulations governing the proper conduct of nonclinical studies involving investigational vectors, as published under Title 21, Code of Federal Regulations (CFR), Part 58. The applicable provisions of the CFR are cited for each violation. The following list of violations is not intended to be an all-inclusive list of deficiencies observed during the inspection:

1. **IHGT failed to manage the testing facility. [21 CFR § 58.31].**
 - A. The Study Director did not fulfill the responsibilities described in 21 CFR § 58.33; see item 2, below.
 - B. The facility does not have an effective Quality Assurance Unit (QAU); see item 3, below.
 - C. Test and control articles have not been appropriately tested; see item 6, below.
 - D. All study personnel are not knowledgeable of their responsibilities as reflected by the deviations described in this letter.
 - E. Deviations from these regulations were not corrected, and documentation of the corrections was not provided in a timely manner or maintained.

2. **The Study Director failed to fulfill the requirements of 21 CFR § 58.33.**
 - A. The Study Director has not noted unforeseen circumstances or deviations that may affect the quality and integrity of nonclinical studies when they occurred, and failed to document what corrective actions, if any, were taken at that time. In several cases, deviations that occurred in studies 98-33, 98-54, and 98-63 were noted six months to more than one year later. Several deficiencies were not documented until the time of the FDA inspection.

For example, there are no records to support the conclusion represented in Amendment #005 to study 98-63. Study personnel did not follow the protocol when changes were reportedly made to study 98-63. Protocol section "VII. Alteration of Design" states the following: "Alterations of this protocol may be made as the study progresses." It was inappropriate for the Study Director to prepare this protocol amendment one year after the study ended in the absence of supporting documentation.

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Your firm's response letter acknowledges that "a limited number of such circumstances and deviations, and resulting corrective actions, were not documented in a timely fashion." We do not agree that these instances were isolated because such deviations were noted in each of the three studies reviewed during the inspection. The inadequate level of documentation for these three studies, which occurred during the period in which IHGT states that it was implementing improvements, casts doubts about the reliability and completeness of the remaining study records. In addition, the deviations were extensive enough that you have determined that study 98-33 must be repeated. For these reasons, FDA

- D
- B. The Study Director inappropriately uses the term protocol "amendment" to describe protocol deviations.
 - C. There is no procedure in place for conducting audits of contracting facilities to determine that the contractors are performing the work according to the testing facility management's expectations and standards.
 - D. •The Study Director did not approve protocol amendments #003 and #004 for study 98-63; these amendments were "approved" by the IHGT Director of Toxicology.

Your firm's response acknowledges this deviation.

- E. The Study Director did not determine whether amendments to protocol 98-63 affected the validity of the study:
 - i. Amendment 1, in which there was a complication during the intra-arterial administration of the vector, and the rest of the test article was administered via another route.
 - ii. Amendment 2, in which there was an increase in injected volume (C of one test vector in study 98-63. The recipient animal(s) received more — in the diluent than did the animals receiving the other test vectors in the study.

Your firm's response letter explains that the Study Director documented this protocol deviation in protocol amendment #002. However, we note that the Study Director did not complete the box marked "Does this affect validity of study protocol?" We acknowledge your firm's promise to standardize the volume and — content of vector preparations in future studies.

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- F. The Study Director did not prepare a protocol amendment to clarify the change in the tissue sectioning methods for study 98-54. There is no documentation of the conversations between the Study Director and the contract laboratory regarding the performance of serial sectioning of the brain for both the vector- and vehicle-injected sites for histopathology evaluation.

Your firm's response states that your firm has documentation regarding the protocol changes. →→ We request that you submit copies of the referenced documentation, including records of all telephone conversations, facsimile transmissions, and electronic messages.

- G. There is no documentation in the files for study 98-33 of the discussion with outside contractor(s) for the preparation and evaluation of the study histology. The Study Director later decided to change contractors after the study had been initiated.

Your firm's response acknowledges this deviation, and states that these records will be maintained in the future.

3. The IHGT Quality Assurance Unit (QAU) does not operate in conformance with applicable regulations. [21 CFR § 58.35].

- A. The QAU monitoring inspections failed to detect, resolve, or document deficiencies in the three studies reviewed during the inspection. Many of the deficiencies noted below were not identified until the time of this FDA inspection. Examples of the QAU deficiencies include, but are not limited to, the following:
- i. Some animals used in studies 98-33 and 98-63 did not meet the protocol-specified weight ranges, as described in item 8, below. There is no evidence that the QAU detected this protocol violation.
 - ii. Study 98-33 animals #1593, #1594, and #1601 were reported as "found dead" by the study pathologist, but the necropsy and clinical pathology records indicate that these mice were sacrificed as scheduled. →→ Please submit copies of the daily observation logs and cage cards for these animals.
 - iii. The necropsy records for study 98-33 indicate that all tissues were taken and preserved at the time of necropsy; however, the pathology report indicates that several key tissues (i.e., pancreas) were missing.
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- iv. Animals #1612 and #1616 in study 98-33 were "found dead" on 1/21/99 according to the daily observations, and tissues were not obtained. The protocol deviation was not noted by the Study Director until 2/21/00 even though the Pathology Report dated 6/14/99 noted the disposition of #1612; animal #1616 is omitted from the Pathology Report.
- v. The pathology report was inconsistent with the necropsy record for study 98-63. The pathology report for animal #AB54 stated that the animal was "found dead" on October 3, 1998, but the necropsy record indicates that the animal was euthanized. This discrepancy was mentioned in the FDA warning letter to your firm dated March 3, 2000. Your firm's responses in this matter have not been substantiated. →→ Please submit copies of the daily observation logs and cage cards for all animals in this study.
- vi. The errors noted in item 9, below, were not detected prior to the FDA inspection.
- vii. The necropsy records for animals #1621 and #1668 in study 98-33 were not signed by the necropsy supervisor.
- viii. The QUA did not detect, resolve, or document the deficiencies in test article characterization described in item 6D, below.

Your firm's response to these items indicate that corrections will be made to the final reports, and that new procedures will be implemented to prevent future deviations. In addition, your firm's response describes that most aspects of study 98-33 were audited several times, and confirms the test article preparation, dilution, and dosing were not audited. Your firm's response describes that the scope of QAU audits will expand in future studies.

- B. The list of current studies provided to the FDA investigators during the inspection is incomplete in that it identifies only those studies that were initiated (signed by the Study Director) after April 10, 1998. The list does not include all the studies for which no final report was written. →→ Our request for a complete list of studies is described in the "Conclusion" section of this letter.
- C. The list described in item 3B, above, contains errors. For example, the In-Life Completion date for study 98-66 indicates that the study duration was more than one year, but the protocol states that the study duration is 'C

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4. Failure to properly store specimens and data. [21 CFR § 58.51].

Raw study data are archived and maintained on open shelves in an unused restroom. There is no individual who is identified as being responsible for maintaining the archived data. Access to the archive area is based on an honor system since all study personnel are issued keys to the room. The facility's practices as described to the FDA investigators during the inspection do not conform to the unapproved/undated version of SOP 4022 or approved (2/16/00) versions of SOP 4022.

Your firm's response letter describes that procedural changes will be implemented to correct this deficiency.

5. IHGT failed to prepare written standard operating procedures (SOPs) as required by 21 CFR § 58.81.

- A. Until February, 2000, there was no approved SOP in place for archiving raw study data that are retained within the facility; see item 4, above.
- B. There were no approved SOPs in place for several critical aspects of nonclinical studies during the period in which studies 98-33, 98-54, and 98-63 were conducted. The following are examples for illustration:
- i. There was no SOP in place at the time of study 98-63 for labeling of tissue samples for histology, both on the outside and inside of the container.
 - ii. There was no SOP in place at the time of study 98-33 for the monitoring of sentinel animals to evaluate the general health of the animals used in the study.
 - iii. The SOP for blood collection from rodents did not provide sufficient detail to reliably educate the personnel involved on the proper techniques for collection, handling, and storage of the samples.

Your firm's response states these SOPs are now finalized.

- C. During the period in which studies 98-33, 98-54, and 98-63 were conducted, there were no approved SOPs for some critical aspects of nonclinical studies.

Your firm's response letter states that "many of its SOPs had not been approved by the QAU, and that some lacked an approved signature or an effective date." It further states that "this first series of SOPs were created in the mid-nineties before the establishment of a QAU."

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- D. There is no standardized definition of critical parameters monitored for a study (i.e., grading of the severity of histologic lesions, and definition of abnormal clinical pathology findings). For example, the pathology report written for study 98-63 underestimates the severity of the liver damage observed in monkeys AB54 and AH45.

Your firm's response states that IHGT has requested the grading criteria used for study 98-63 from the contract pathologist. →→ Please submit this information with your response to this letter.

Your firm's response letter further describes that the slides from these animals will be "peer-reviewed" and that the information will be included in the raw data and in the final report. The response also describes that you will develop a new SOP to provide instructions in cases where the pathology results are inconsistent with the pre-defined criteria or the histopathology report.

- E. The contracting laboratories used by IHGT do not provide definitions for specific tests included in a study (i.e., normal limits for clinical pathology values in rodents). In cases where your firm is relying on reference data (e.g. published literature, reference standards), the citations for those references are not documented with a memorandum to the file.

Your firm's response letter describes that IHGT conducted a study for the purpose of developing normal ranges for the _____ strain of mouse. →→ Please describe the techniques used to obtain the specimens for the study in the absence of an SOP for the procedure; see item 5Biii, above. →→ Please submit the protocol and results of your firm's normal range study in _____ mice. Were the results audited?

- F. There were no procedures in place (in an SOP or in the study protocol) to standardize the handling of the animals during the magnetic resonance imaging (MRI) examinations in study 98-54. It is possible that variations in the manner of animal handling and MRI procedure could affect the results of the MRI testing. There were no written notations regarding the type and amount of anesthesia used for the animals, or other details about the transport of animals to the hospital MRI facilities.

Your firm's response letter states that this information will be provided in the final report from the individuals who performed these portions of the study. In the absence of contemporaneous documentation, CBER does not have confidence that the final report can accurately and completely describe these operations more than 18 months after the study was conducted.

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- G. At the time of study 98-63 there was no provision to request an outside consultant or additional review to resolve outstanding issues (such as the example listed in 5E, above).

Your firm's response letter states that new procedures will be developed to correct these deficiencies.

**6. IHGT failed to characterize the test and control articles.
[21 CFR § 58.105].**

- A. The vector H5.001CBhOTC was used in study 98-63 25 months after the preparation date. The study protocol specified that expiration date of the test articles was _____ months from the date of preparation. There is no documentation to support the stability of the vectors stored longer than _____ months.

A memorandum dated January 27, 2000, written by the former Associate Director of the Translational and Clinical Research Program, states "the rate of decay of infectivity is actually very slow, with an approximate _____ Thus it is likely that the adenoviral vectors have retained a great deal of activity even after _____ months of storage."

* This memorandum would indicate that the animals who received a vector stored for 25 months would have been given a dose of vector from 52.2% to 65.6% below the vector dose specified in the protocol. This reduced dose of vector could result in an under-estimation of toxicity in the animal studies used to establish the dose of vector to be administered to human subjects. We note that the specific lot of this vector used in the clinical studies to treat human subjects _____ was stored for only 2 months prior to its administration. Although this vector was the same for the monkey study and the human study, the lots were not prepared at the same time, and the stability of the stored lots could be very different.

Your firm's response letter states that "recently completed stability testing of adenoviral vectors indicates that these vectors are stable when stored in _____" This statement contradicts information in the January 27, 2000, memorandum described above. →→ Please submit the referenced stability protocols. →→ Please provide the results of all stability testing for each vector included in the table requested in the "Conclusion" section of this letter. If stability testing was not performed, your response should so state.

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In addition, your firm's response letter also states that "in the future, references to expiration date will not be included for studies in support of a Phase I clinical trial." →→ Please explain if this means that the expiration date for vectors in future nonclinical studies will be — months. We do not support the elimination of test article expiration dates from study protocols.

- B. The vector dilution was not performed in a consistent manner for the three groups in study 98-63. The volume required for the dose of vector H5.001CBhOTC was greater than the — volume specified in the protocol. See item 2Eii, above.
- C. There are no characterization data or acceptance criteria on file for the lot of vector — used in study 98-54. The vector dilution records state that the stock was from — prepared —. The vector was first used on — which is less than two weeks after the preparation date even though, at the time, the specific characterization assays required from — to be completed.

Your firm's response states that the characterization data "were on file as a memorandum in the Human Applications Laboratory (HAL)." →→ We request that you submit this memorandum and the supporting raw data sheets for our review.

We acknowledge your firm's explanation that the release criteria adopted in 2000 are different from those in place in December 1998. →→ Please submit an explanation of the differences in the release criteria and when the changes were adopted.

- D. The dilution records for virus preparation were inadequate for studies 98-33, 98-54, and 98-63 in that the following information was not documented:
- i. Identification numbers of the animals to receive the test or control article.
 - ii. Dosages of test article and control article administered.
 - iii. Concentrations of vector stock prepared for the studies.
 - iv. Lot numbers of the vectors.
 - v. Dates of preparation of the test/control articles.
 - vi. Numbers of stock vials needed with their reference numbers.
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- vii. Certificates of analysis and/or lot numbers for any materials used as vehicles for dilution or for vehicle controls.
- viii. The vector release sheets for study 98-33 consist of handwritten notes with no signature.
- ix. Preparation and dilution of vector complex for study 98-33.

Your firm's response letter acknowledges the deficiencies for study 98-33. The letter disagrees with the observations for studies 98-54 and 98-63, stating that the information was documented, even though such documentation was not available at the time of the FDA inspection of your firm. The response also describes a new SOP for documenting this information in future studies. →→ Please submit copies of the documentation cited in your firm's response letter for distribution and use of the vectors for studies 98-54 and 98-63. →→ Please submit a copy of the final revised SOP for these activities.

**7. IHGT failed to document test and control article handling.
[21 CFR § 58.107].**

- A. There is no documentation concerning the following aspects of handling of the test and control articles in studies 98-33, 98-54, and 98-63:
 - i. Time of vector preparation.
 - ii. Time of delivery to the Translational Research Program.
 - iii. Time of completion of vector treatment of the animals recorded on the vector preparation sheet. This is especially important for the product in 98-33 because there was a _____ limit on the stability of the complexed vector test article.
- B. There is no record of the amount and disposition of any returned test/control articles required by the protocols for three studies.

Your firm's response acknowledges that there were deficiencies in documentation, and that these will be corrected through the implementation of new SOPs.

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**8. IHGT failed to conduct the study according to the protocol.
[21 CFR § 58.120].**

- A. Animals that did not meet the protocol-defined body weight ranges were used in studies 98-33 (—) and 98-54 (—). There was no written justification as to why these animals were used.

Your firm's response acknowledges these deviations, and describes procedures that will be instituted to screen animals for inclusion in future studies.

- B. The necropsies of animals #1571, 1605, 1654, 1655, 1660, 1661, 1662, 1668, and 1669 were not conducted according to the protocol for study 98-33. These errors were not reported to the study pathologist who reported that these animals were sacrificed as scheduled in the protocol.

Your firm's response describes this as an error in the draft histopathology report, but it does not address the issue of performing the necropsies at time points not specified in the protocol.

- C. Dr. Wilson signed protocol amendments #001 and #002 for study 98-33 in the signature block for Study Sponsor even though he was not the sponsor of the study. There is no record that the sponsor signed these protocol amendments. The protocol states "No changes in the protocol will be made without the consent of the Study Director and Study Sponsor. In the event that the Study Director must implement a protocol change, such changes will have written authorization. All protocol modifications will be signed by the Study Director and Study Sponsor."
- D. There was no signature block for Study Sponsor signature for protocol amendment #010 for study 98-33. This protocol amendment changed the contractor originally selected to perform the histological evaluations for the study. The protocol amendment notes that the new contracting laboratory "is not fully GLP compliant."

- E. Gonadal tissue was not obtained from the first two animals on study 98-54 even though the protocol required these tissues "for | C"

Your firm's response indicates that these errors are documented in "protocol amendments," and that new procedures will be implemented to clarify the tissues to be collected at necropsy. These errors should be described as protocol deviations rather than protocol amendments.

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- F. The Study Director did not promptly amend study 98-63 to account for the discrepancy between the _____ committed for the study (protocol amendment #001) versus the _____, as described in the draft final report; see also item 2A, above.

9. IHGT did not accurately record study data. [21 CFR § 58.130(e)]

- A. The vector dilution records and the logbook for the MRI assessments inaccurately report some animal identification numbers.

Your firm's response letter acknowledges the errors and proposes changes to verify that the log book information is correct.

- B. The animal treatment records for monkey #AC3B contain errors in the sample collection information on days _____ on study 98-54 [] At the time of the FDA inspection, these errors were not corrected or documented in the file.

Your firm's response letter acknowledges these errors, but describes them as unusual. We do not agree with your position that these errors are isolated since errors were found in all three studies reviewed during this FDA inspection.

10. IHGT failed to prepare final reports of nonclinical laboratory studies. [21 CFR § 58.185].

IHGT has not prepared final audited reports for any of the _____ nonclinical studies conducted since 1998. This figure is based on a list of studies initiated after April 10, 1998, that was provided to FDA during the inspection. This listing does not include several studies that were submitted to FDA in support of human clinical trials, but for which no final audited report was submitted, including the following: 94-2, 94-3, 94-9, 95-5, 95-8, 95-9, 95-10, 95-15, 95-17, 96-1, 96-13, 96-17, 96-18, and 96-19. This is an incomplete list of studies described in only one of your firm's Investigational New Drug Applications (INDs).

Your firm's response letter states that you are in the process of drafting final reports "for almost all of the studies conducted during 1998 and 1999." As noted in the "Conclusion," below, FDA may []

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11. IHGT failed to maintain study documentation. [21 CFR § 58.190].

- A. The test facility could not provide the following documentation during the inspection:
- i. Sentinel monitoring results for study 98-33.
 - ii. Health reports from the animal supplier for study 98-33.
 - iii. Necropsy records for two animals from study 98-33.

Your firm's response cites new procedures that will improve the documentation of future studies.

- B. The reports for the clinical pathology data from the contractor were not up to date in the files for study 98-54. There was no documentation of communication from your facility requesting the updated reports from the contractor.

Your firm's response letter describes that there is documentation of the contacts with this contractor, but that the documentation is not included in the study file. Your firm could not locate these records during the inspection, and did not provide them in your firm's response letter.

**12. IHGT failed to retain samples of control and test articles.
[21 CFR §§ 58.195(c) and 58.105(d)].**

There was no archive of retained samples of the test articles as specified in protocols for studies 98-63, 98-54, and 98-33.

Conclusion

Your firm's response states that "since 1998 IHGT believes it has made — and continues to make— enormous strides in the manner in which it conducts and documents its toxicology studies." We conclude from our inspection that studies 98-33, 98-54, and 98-63 were not conducted in accordance with GLP regulations.

Based on the deficiencies revealed by this inspection, CBER does not agree that it will be feasible to accurately reconstruct the studies from the available records. For these reasons, FDA may

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→→ Please submit a listing of **ALL** animal studies conducted by IHGT from 1994 to the present, and include the following information: study number, study title, test article, test system, nature of study, study initiation date, in-life start date, in-life completion date, and Study Director. Please identify the sponsor for each study, and the dates of the draft final report and audited final report. Please provide a printout that includes complete information for each field. Please identify whether each study was intended to be performed in accordance with GLP requirements, or whether the studies were of an exploratory nature. Please identify to which IND each study was submitted where your firm is the Study Sponsor.

The deficiencies observed during this inspection require corrective action. We request that you inform 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 action cannot be completed within 15 business days, state the reason for the delay and the time within which the corrections will be completed. We will review your response and determine whether the actions are adequate. This letter does not preclude the possibility of a corollary judicial proceeding or administrative action concerning these violations.

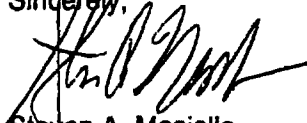
→→ You must notify each external Study Sponsor that the nonclinical studies performed by your facility were not conducted in accordance with the GLP regulations. Please provide us with a copy of each notification.

Please send your written response to:

Patricia Holobaugh (HFM-664)
Division of Inspections and Surveillance
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
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

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