DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

DEC 21 1999

The Honorable Henry A. Waxman
U.S. House of Representatives
Washington, D.C. 20515

Dear Mr. Waxman:

I am responding to your November 23 letter in which you expressed concern about the death of a patient in a University of Pennsylvania gene therapy protocol and the adequacy of National Institutes of Health (NIH) oversight and public scrutiny of clinical gene transfer protocols. Although gene therapy research, like any form of clinical research, poses potential risks to research subjects, the NIH is committed to minimizing risks and ensuring that patients are fully informed of such risks. As gene therapy research develops, so does our knowledge about any risks associated with it. To this end, the NIH makes every effort to ensure that the gene therapy clinical trials we support are safe and in conformance with Federal guidelines and regulations.

In light of recent events, the NIH is taking a number of steps to ensure that gene therapy investigators are following its rules for the conduct of human gene transfer studies. Before addressing your six specific questions, I would like to describe those steps as well as several other measures the NIH has initiated to ensure the appropriateness of NIH oversight of clinical gene transfer research.

- In response to the death of the patient at the University of Pennsylvania, the NIH sent a letter on October 1, 1999, to all principal investigators using the same or similar method of gene delivery, requesting safety and toxicity data, including adverse events. A working group of the Recombinant DNA Advisory Committee (RAC) was formed to conduct an in-depth analysis of the data and, if necessary, develop guidance regarding the use of adenoviral vectors in gene transfer studies. The working group carried out a comprehensive scientific review and public discussion of the data at a scientific symposium held on the first day of a three-day RAC meeting December 8-10, 1999. The preliminary recommendations of the working group relate to the need for standardization of adenoviral vector production and quality control as well as additional patient selection criteria and monitoring procedures. The RAC will develop a final report of its conclusions and recommendations on the use of adenoviral vectors in human gene transfer research. If it determines that further guidance is needed regarding the use of adenoviral vectors, a proposal will be issued for public comment. After consideration of the public comment, the RAC will transmit recommendations to the NIH Director. If approved by the Director, this guidance will be incorporated into the *NIH Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*).

- The *NIH Guidelines* currently require that any serious adverse event that occurs during the course of a gene therapy clinical trial be reported immediately to the NIH. The NIH and the Food and Drug Administration (FDA) have established a new notification process for serious adverse events whereby FDA notifies the NIH when it receives serious adverse event reports from investigators and sponsors. The NIH can thereby verify whether it has received the same reports and, if not, can follow-up with investigators. One of the main goals of this information exchange is to enhance investigator compliance with the *NIH Guidelines*. The entire gene transfer research community was notified of the establishment of this process in a November 5, 1999, letter from the FDA (enclosed at Tab I).

- In November, NIH issued a memorandum (enclosed at Tab II) asking all institutions conducting human gene transfer research to review their institutional policies and procedures to ensure compliance with the *NIH Guidelines*. The memorandum restates the requirements for serious adverse event reporting, directs institutions to ensure that they are in compliance with these reporting requirements, and requests that any institution not in compliance notify the NIH Office of Recombinant DNA Research within 15 days. A copy of the memorandum was sent to all Institutional Review Boards, Institutional Biosafety Committees, and Principal Investigators at institutions conducting human gene transfer studies.

- To further ensure that all pertinent information regarding the safe and ethical conduct of human gene transfer trials is provided to the RAC for timely review and analysis and, as necessary, public discussion, the NIH published proposed amendments to the *NIH Guidelines* in the November 22, 1999, *Federal Register* for public comment (enclosed at Tab III). During the December RAC meeting, the proposed amendments were reviewed and public comments discussed. The discussion and comments focused on the scope of the reporting requirement, confidentiality of this information, burden and consequences of reporting, and resources necessary to provide appropriate review and public discussion of the reports. The RAC determined that further exploration was necessary of the issues related to the scope and time frame of reporting and the value of harmonizing NIH and FDA requirements. A working group of the RAC will be meeting shortly to consider these issues and to formulate recommended changes to the *NIH Guidelines*. The RAC expects to transmit a final recommendation to the NIH Director early next year.

- In December 1999, the NIH Director established a working group of the Advisory Committee to the Director (ACD) to review the role of the NIH in oversight of clinical gene transfer research. The Working Group is being encouraged to consult with other experts and solicit public comment in the course of its work. It is asked to develop recommendations to address the following questions: 1) Is the current NIH framework for

oversight and public discussion of clinical gene transfer research appropriate, especially with regard to the respective roles of the RAC and the *NIH Guidelines*; 2) Are current NIH mechanisms adequate for coordination of the oversight of clinical gene transfer research with those of the FDA, the OPRR, the IRBs, and the IBCs; 3) Are additional NIH measures needed to minimize the risks associated with clinical gene transfer research; and 4) What should be the NIH role in regard to reporting, analysis, and public discussion of serious adverse events?

I will now address each of your six specific questions in turn.

1. *On November 5, 1999, the members of the RAC empaneled in December 1995 wrote to you and Secretary Shalala that during their review of the University of Pennsylvania protocol, "FDA assured RAC members that there would be a feedback loop from the non-public FDA review process and that any major changes in protocols reviewed by the RAC would be reported to the RAC." It is clear that such "feedback" never took place between the RAC and the FDA. Please explain the reasons for this failure.*

During its December 9, 1996, meeting, the Recombinant DNA Advisory Committee discussed the importance of receiving reports regarding the extent to which its recommendations were incorporated into an investigator's final FDA-approved protocol. Although a proposal was considered to have FDA provide information about changes to the final protocol, in the final analysis, it was concluded that the responsibility for reporting to the RAC regarding protocol changes should remain with the investigator and/or the sponsor. The RAC recommended that this additional responsibility be added to the *NIH Guidelines*. A public notice and comment period were provided and final language was added to the *NIH Guidelines* at Appendix M-VII-A and announced in the October 31, 1997, *Federal Register*. Appendix M-VII-A reads as follows:

> *Upon receipt of notification of permission to proceed with an Investigational New Drug application for a human gene transfer protocol, the Principal Investigator(s) shall submit a written report that includes the following information: (1) how the investigator(s) responded to RAC recommendations on the protocol (if applicable), and (2) any modifications to the protocol as required by FDA.*

Notwithstanding the importance of holding investigators responsible for reporting information about protocol changes and other matters relevant to the ongoing safety of gene transfer studies, FDA and NIH have agreed that information sharing by the agencies will enhance the work of the RAC in monitoring scientific, ethical, and safety issues in gene transfer studies. To this end, on December 7, 1999, FDA issued two new Standard Operating Procedures to institute weekly notification of NIH of reports of adverse events and any other changes in gene therapy protocols received by the FDA (enclosed at Tab IV).

2. *On May 14, 1996, Dr. Thomas Shih in the NIH Office of Recombinant DNA Activities (ORDA) wrote to Dr. Mark Batshaw, a principal investigator of the University of Pennsylvania protocol, that "the RAC will no longer be engaged in case-by-case review of human gene transfer protocols. No approval from the NIH director is required for initiation of human gene transfer experiments. The new NIH policy became effective as of the date May 9, 1996." The letter also states that "the investigators whose protocols have been previously approved by the RAC with stipulations are not required to submit to ORDA additional data for the fulfillment of the stipulation requirements." In waiving the RAC's right to "additional data" from the University of Pennsylvania protocol, the letter preceded the July 8, 1996 NIH Federal Register notice by a full month. It also directly contradicts the preliminary nature of the July 8 notice, as well as the final policies established in the November 22, 1996, Federal Register notice. Why did NIH issue this apparently premature and inaccurate letter? To whom else was this letter sent?*

Yes, the May 1996 letter to the University of Pennsylvania was inaccurate. These changes to the NIH oversight process were first proposed in July 1996 in a Federal Register Notice and were ultimately adopted in modified form in the *NIH Guidelines* on October 31, 1997, after significant public review and comment. To this end, it is important to note that a copy of the July 8, 1996, *Federal Register* Notice was mailed to *all* registered gene therapy investigators immediately upon its release to ensure that the research community was fully aware of the proposed changes and to encourage them to submit comment. The NIH is reviewing the circumstances under which the May 1996 letter was sent.

A total of seven principal investigators, whose protocols were pending approval by the NIH Director at the time, received such letters. Five of the protocols had received RAC approval contingent on the fulfillment of specific RAC stipulations related to the provision of additional information and/or data. Two of the protocols did not meet the criteria to undergo public RAC review and were exempt. Six of the seven letters were signed by Dr. Nelson Wivel, who was, at the time, Director of ORDA. The letter to Dr. Batshaw was signed by Dr. Shih, an ORDA staff member, at the request of Dr. Wivel. Dr. Wivel had recently accepted a position with the Institute for Human Gene Therapy at the University of Pennsylvania. In addition, a memorandum containing the same information was sent to all investigators involved in clinical gene transfer research. Copies of the seven letters, the memorandum, and the *Federal Register* Notice are enclosed at Tab V.

3. *In its November 22 Federal Register notice, the NIH announced it would maintain a "publicly available, comprehensive NIH database of human gene transfer clinical trials, including adverse events." Such a database was intended to ensure that, in lieu of RAC protocol approval authority, gene therapy adverse event reports would be publicly*

available. Has the NIH created such a database? If not, why has NIH failed to fulfill this commitment to public disclosure and oversight of gene therapy protocols?

An electronic database of clinical gene transfer trials will enhance oversight and public awareness of developments in gene transfer research. After exploring the possibility of a joint database with FDA, NIH began planning in FY 1996 for the development of its own Human Gene Transfer Information System (HGTIS). HGTIS will contain current information about all gene transfer clinical trials in the U.S. The information will describe the key components of each protocol as well as safety and efficacy data. The ultimate goal of the database is to enhance awareness of new developments in gene transfer research and to disseminate important safety information to the general public, patients, and the scientific community. Phase I of the database is expected to be completed toward the end of 2000.

Although the electronic database is not yet operational, it is important to note that the dissemination of information on gene transfer occurs regularly through the RAC public review process. At each meeting of the RAC, current data on human gene therapy trials are discussed in public session. The data reviewed include the distribution of trials according to mechanisms for gene delivery, the diseases or conditions being treated, and any serious adverse events reported. This comprehensive review of data by the RAC is a critical component of Federal oversight of gene transfer research and fosters broad public awareness of issues and developments in human gene transfer research. The information also is available upon request to investigators and other members of the public.

4. *The principal investigators of the Vascular Genetics and the GenVec/Parke-Davis gene therapy protocols have reportedly requested that adverse event reports of deaths and illnesses from the protocol be withheld from the public. Such a request was reportedly also made by Schering-Plough, the sponsor of other gene therapy protocols. Did the NIH comply with these requests? Please provide copies of these and any other comparable requests, as well as documentation of the NIH's decisions and background concerning the protocols.*

There are four instances in which adverse event reports submitted to NIH were marked confidential. These involve reports submitted by Dr. Ronald Crystal, New York Hospital-Cornell Medical Center, whose clinical trial sponsor was GenVec, Inc., and Dr. Nicholas J. Pelliccione, Senior Director, CMC, Worldwide Regulatory Affairs, Schering Corporation. Although the RAC was able to receive copies of the reports on a confidential basis, the labeling of the reports precluded public discussion of the events by the RAC. Copies of Dr. Crystal's letter and the adverse event reports from Dr. Pelliccione are enclosed at Tab VI. NIH has not received adverse event reports labeled confidential from Vascular Genetics, Inc.; GenVec, Inc.; or Parke-Davis, Inc. The protocols in which the reported adverse events occurred are:

A Phase I Study of Direct Administration of a Replication-Deficient Adenovirus Vector (Ad_{GV}VEGF121.10) Containing the VEGF121 cDNA to the Ischemic Myocardium of Individuals with Life Threatening Diffuse Coronary Artery Disease (NIH Protocol # 9711-221) (Crystal/GenVec)

Gene Therapy of Primary and Metastatic Malignant Tumors of the Liver Using ACN53 Via Hepatic Artery Infusion: A Phase I Study. (NIH Protocol # 9412-097) (Schering-Plough, Inc.)

A Phase II/III Trial of Chemotherapy Alone Versus Chemotherapy Plus SCH 58500 in Newly Diagnosed Stage III Ovarian and Primary Peritoneal Cancer Patients with $\geq$0.5 cm and $\leq$2 cm Residual Disease Following Surgery (NIH Protocol # 9901-280) (Schering-Plough, Inc.)

A Phase II Study of SCH 58500 in Combination with Chemotherapy Alone in Patients with Colorectal Cancer Metastatic to the Liver (NIH Protocol # 9905-318) (Schering-Plough, Inc.)

Documentation of the RAC's decisions with regard to these protocols is enclosed at Tab VII.

NIH is taking steps to strengthen the *NIH Guidelines* with respect to this issue. At the September 2-3, 1999, meeting of the RAC, NIH proposed a plan for addressing its concerns about the increasing number of adverse event reports that were labeled confidential. A copy of the draft minutes of the September RAC meeting is enclosed at Tab VIII. The plan involved adding language to the *NIH Guidelines* that would require "that serious adverse event reports must not contain any trade secret or commercial or financial information that is privileged or confidential and that all information submitted in accordance with the *NIH Guidelines* will be considered public unless NIH determines that there are exceptional circumstances." The proposed language was published for public comment on November 22, 1999, discussed at the December meeting of the RAC, and is currently under further RAC review.

5. *On November 5, 1999, Dr. Kathryn Zoon, Director of the FDA Center for Biologics Evaluation and Research, issued a letter to gene therapy sponsors and principal investigators, stating that "investigators/sponsors are expected to report all serious adverse events to both the FDA and NIH." Have all such adverse events been reported simultaneously and in a timely manner to both agencies in the past? Please identify any cases where gene therapy investigators or sponsors have failed to comply with this regulatory requirement.*

Thus far, our analysis of this issue is based on data received in response to NIH's request for adenoviral safety and toxicity data, a step we took as a result of the reported death. Of the 691 serious adverse events reported, 39 had been reported previously as required by the *NIH Guidelines*. A more comprehensive assessment of compliance will be possible as a result of responses to the November 22, 1999, memorandum to all institutions conducting gene transfer trials. In addition, NIH and FDA have initiated a comparative analysis of the number of serious adverse events in human gene therapy studies reported to each agency. This analysis will provide important information about how well investigators comply with Federal requirements to report serious adverse events. It will also enable a comprehensive review of the adverse events themselves to determine whether any are due to the gene therapy rather than the natural progression of the underlying disease.

6. *Dr. Zoon also stated that "FDA will notify NIH/ORDA of the receipt of an adverse event report on a gene therapy IND to enhance investigator compliance with the NIH Guidelines." Is the NIH aware of cases in which the FDA has possessed such adverse event reports, but has delayed or failed to notify NIH of these reports? Has FDA cited trade secrecy to NIH or the RAC as a basis for its failure to comply with this regulatory requirement? Please specify which, if any, protocols and adverse event reports were involved.*

As a general rule, FDA regulations require the maintenance of confidentiality of data and information contained in an Investigational New Drug (IND) application for all biological products, including those submitted in human gene transfer experiments, under the provisions in 21 CFR 601.50 and 601.51. The NIH and FDA are committed to ensuring continued public awareness of human gene transfer research adverse events, and the agencies are currently working closely together to ensure an effective and harmonized Federal oversight system. Examples of recent efforts include:

As described earlier, on November 5, the Director, Center for Biologics Evaluation and Research (CBER), notified gene therapy IND sponsors and principal investigators of the process for the submission of gene therapy INDs and any subsequent adverse event reports to CBER and how that process relates to the submission of gene therapy protocols and adverse event reports to the NIH, as required by the *NIH Guidelines*;

The FDA Commissioner issued a memorandum on December 1 (enclosed at Tab IX) to the Associate Commissioner for Public Affairs regarding FDA's intended disclosure of summary data on safety and effectiveness related to a clinical study of gene therapy in participants having ornithine transcarbamylase (OTC) deficiency and FDA's participation in the December 8-10 public deliberation of the University of Pennsylvania's ornithine transcarbamylase (OTC) deficiency protocol;

As described earlier, on December 7, FDA issued two new Standard Operating Procedures to institute weekly notification of NIH of adverse events in gene therapy protocols and any changes in gene therapy protocols received by the FDA.

The NIH appreciates your interest in its efforts to ensure that patients who participate in human gene therapy clinical trials are fully informed and protected and that the public is fully aware of developments in human gene transfer research. We will continue to review the circumstances involving those human gene therapy trials in which adverse events were not reported and will strengthen our requirements if appropriate. We share the common goal of ensuring the safety and well being of patients enrolled in gene transfer trials. The NIH looks forward to working with you as our efforts continue.

Sincerely,

Harold Varmus, M.D.
Director

Enclosures

Tab I	November 5, 1999, letter from the FDA
Tab II	November 22, 1999, NIH memorandum to ICs
Tab III	November 22, 1999, *Federal Register* Notice
Tab IV	December 7, 1999, FDA Standard Operating Procedures
Tab V	Seven letters, a memorandum, and the July 8, 1996, *Federal Register* Notice
Tab VI	Dr. Crystal's letter and the adverse event reports from Dr. Pelliccione
Tab VII	Documentation of the RAC's decisions on protocols
Tab VIII	Draft minutes of the September 1999 RAC meeting
Tab IX	December 1, 1999, FDA memorandum to the Associate Commissioner for Public Affairs