DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

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

Dear Mr. Waxman:

I am writing to address additional questions raised in your January 10 letter about the oversight by the National Institutes of Health (NIH) of clinical gene transfer protocols. Your questions are in follow up to your previous inquiry.

First and foremost, let me assure you that I certainly concur that the NIH must take immediate steps to ensure that our oversight of gene transfer research is exemplary. In our earlier correspondence, we outlined a number of steps we are taking to address problems, and we will continue to keep you apprised of our progress.

With regard to the NIH's oversight of gene transfer research, the NIH is convening a working group of the Advisory Committee to the Director, NIH, to examine the current NIH framework for oversight and public discussion of clinical gene transfer research, especially with regard to the roles of the Recombinant DNA Advisory Committee (RAC) and the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*. The working group is being asked to examine several options for NIH oversight, and among them is re-establishing RAC approval of novel protocols. The working group will be holding its first meeting next month, and it will meet again in March in conjunction with the RAC. We hope to receive final recommendations from the working group in May.

An important component of oversight is knowledge of the potential safety concerns associated with gene transfer research. In this regard, and as discussed in further detail below, the RAC is expected to discuss its recommendations regarding NIH requirements for serious adverse event reporting at its next meeting in March.

The NIH is committed to its oversight responsibilities in gene transfer research. To this end, the Office of Biotechnology Activities (OBA) (formerly the Office of Recombinant DNA Activities) has, and has had, the necessary resources to conduct its present responsibilities, and will receive any additional resources required to meet any new or expanded responsibilities. For example, recently, the OBA has taken on responsibility for two Secretarial-level committees on genetic testing and xenotransplantation. Contrary to press reports, OBA's budget and personnel increased significantly attendant to these new responsibilities. In addition, as the field of gene transfer has grown in the last few years, the

OBA budget and personnel have grown concomitantly. The OBA is currently recruiting additional staff to enhance management of clinical protocol submissions, amendments, and annual reports; analysis of serious adverse event reports; review of vector safety issues; educational programs for gene transfer research investigators; and database management.

With regard to NIH's responsibility to ensure public access to data on gene transfer research, the NIH has been working diligently to develop an interactive web-based database. The database is designed to enable users to search for specific variables, analyze aggregate data, and identify emerging trends in gene transfer research. This task has proven to be difficult and highly complex, particularly in light of the multiple audiences that are expected to use this resource. Our goal is to develop an electronic resource that both the general public and the scientific community will be able to easily access and use to obtain current information about specific protocols, including information about adverse events and developments in gene transfer research. The first phase of the database will be publicly available by the end of this year. In subsequent years, we will evaluate the first phase of the database and, as necessary, refine elements which do not meet user expectations.

It is, however, important to emphasize that all of these data, including adverse event reports, are made available in the public domain, once they have been received to the NIH. Comprehensive information on all human gene transfer trials registered with the NIH since the inception of the *NIH Guidelines* is now, and always has been, publicly available. At each RAC meeting, a portion of the agenda is devoted to the presentation of clinical gene transfer trials that have been registered with the NIH, as well as a presentation of any serious adverse events that have been reported since the previous meeting. A copy of each new proposal is available to the public at all times. In fact, the NIH provides a copy of any proposal submitted to the NIH upon request by an investigator or by a member of the public. In addition, information on gene transfer protocols and data reviewed at each RAC meeting are posted on NIH's Web site, http://www.nih.gov/od/oba/. This includes discussions of novel protocols, a list of registered protocols, core information about each protocol--elements such as the protocol title, trial site, principal investigator, disease under study, and vector being used for the gene transfer--and any reported serious adverse events.

You also asked me to comment on the failure of investigators doing clinical gene transfer to comply with requirements for reporting all serious adverse events to the NIH and to provide additional information about the causes of these events. Like you, we are deeply concerned about the under-reporting of serious adverse events to the NIH, and we are taking steps to address this problem expeditiously.

The *NIH Guidelines* clearly place the responsibility for reporting all serious adverse events on the investigator and on the institution. In addition, all investigators who register a protocol with the NIH receive a letter from the NIH reminding them of their obligations under the *NIH Guidelines* to report all serious adverse events. Even though these reminders are explicit and

targeted to each investigator, they clearly have not accomplished what we intended. The failure of investigators and institutions to comply with this requirement must be shared by the NIH itself. We were receiving only a small number of adverse event reports and we certainly should have recognized this as a sign of under-reporting.

Why have investigators failed to report serious adverse events and what are we doing to ensure future compliance with the *NIH Guidelines*? Despite the clearly stated NIH requirements for adverse event reporting in *the Guidelines*, we believe that non-compliance was, at least to some extent, the result of confusion on the part of many investigators and institutions regarding the significant differences between the NIH and the FDA requirements. Nevertheless, while this is an explanation for inadequate reporting, it is not an excuse. We must be sure that this does not happen again. Greater efforts to ensure that investigators and institutions are cognizant of their responsibilities are clearly needed, and the NIH is dedicating additional resources to educating both about their responsibilities and obligations under the *NIH Guidelines*.

According to the *Guidelines*, as a result of non-compliance, the NIH can suspend, limit or terminate NIH funds for a particular gene transfer project or for all recombinant DNA research at an institution. The NIH can chose to impose a requirement for prior NIH approval of any or all recombinant DNA projects at an institution. We can also conduct site visits to ensure that institutions have the proper processes in place to comply with the *Guidelines*. To this end, the NIH Office of Extramural Research will undertake a series of site visits to NIH funded institutions to assess the level of understanding of NIH rules and to identify any problems associated with NIH oversight, paying particular attention to compliance with the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, as well as to financial conflicts of interest.

We have taken several immediate steps. First, we sent a memorandum to institutions conducting human gene transfer research directing them to review their institutional policies and procedures for ensuring compliance with the *NIH Guidelines* and requested that any institution that found compliance problems notify the NIH. A copy of the memorandum was sent to Institutional Review Boards, Institutional Biosafety Committees, and principal investigators at institutions conducting human gene transfer studies. We are in the process of reviewing responses to the memorandum and are following up with institutions, as necessary.

Second, the FDA established a new process for sharing information with NIH and notified the gene transfer research community of this change in a November 5, 1999, letter. The FDA formalized the process in two new Standard Operating Procedures and Policies (SOPPs). The SOPPs, which were issued December 7, 1999, institute weekly notification to NIH of reports of adverse events and any other changes in gene therapy protocols received by the FDA. While these new SOPPs will enhance the ability of NIH to monitor serious adverse

events, in no way will they diminish the responsibility of investigators to fulfill their reporting requirements to NIH.

Third, a working group of the RAC is reassessing the current requirements for the scope and timing reporting of adverse events to the NIH, especially with respect to the current differences between the adverse event reporting requirements of the NIH and the FDA. The working group proposal will be discussed at the next RAC meeting in early March.

Fourth, the NIH, with concurrence from the RAC, is taking steps to prevent sponsors from circumventing public access to adverse event reports by labeling this information proprietary. The RAC articulated its strong objection to this practice, highlighted the importance of ensuring patient confidentiality to the greatest extent possible, and recommended changes in the *NIH Guidelines* to ensure public access to adverse event reports.

Finally, in regard to whether the change in the approval function of the RAC contributed to the under-reporting problem, it is important to point out that the RAC's role in protocol approval has no bearing whatsoever on the obligation of investigators and institutions receiving NIH funds for recombinant DNA research to comply with the clearly stated reporting requirements set forth in the *NIH Guidelines*.

You also asked to have an update on NIH's investigation of the circumstances of the issuance of the May 14, 1996, letter. Because of the seriousness of this matter, we have referred it to the Office of the Inspector General in the Department of Health and Human Services for further review. Of note, between May 1996 and October 1997, the review and approval of protocols deemed novel by the RAC did not change.

Finally, you also requested that I comment on whether the public interest would be better served by moving the RAC and OBA to the Office of the Secretary (OS), similar to the transfer of the Office for Protection from Research Risks (OPRR). The NIH agreed that the transfer of OPRR to the OS was appropriate. There are significant differences, however, in the roles and responsibilities of OBA, the RAC, and OPRR and, therefore, important reasons for the RAC to remain within the NIH umbrella. The *NIH Guidelines* govern not only investigators who receive NIH funding for gene transfer research, but also investigators conducting gene transfer research at institutions that receive funding from NIH to perform research involving recombinant DNA. Public accountability via the *NIH Guidelines* is a result of NIH funding, which provides a direct enforcement authority. The authority to enforce compliance with the *NIH Guidelines* should remain connected to the funding entity. Most importantly, gene transfer research is highly experimental and must remain close to the science enterprise and those who administer it. OBA benefits by being closely connected to the research activities of the NIH, since NIH staff help keep OBA and the RAC apprised of emerging scientific developments, provide input into the development of agendas for scientific conferences, and identify issues for RAC consideration. Finally, one of the

principal reasons for locating OPRR outside the NIH was to strengthen its ability to interact with other agencies within DHHS and with other Departments. In the case of gene therapy studies, NIH has a strong working relationship with the FDA and, in response to specific problems regarding under-reporting of adverse events, new procedures have been instituted to further enhance interagency communication. Moreover, FDA and other governmental agencies are represented on the RAC.

Thank you for your continuing interest in our efforts to ensure that NIH's oversight role in gene transfer research is effective and appropriate. We welcome your interest and appreciate your continued support of our efforts. We will keep you apprised of our progress.

Sincerely,

Ruth L. Kirschstein

Ruth L. Kirschstein, M.D.
Acting Director