STATEMENT OF

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Mr. Chairman and Members of the Subcommittee, I am Amy Patterson, the Director of the Office of Biotechnology Activities at the National Institutes of Health (NIH). The NIH's oversight of human gene transfer research is embodied in the activities of the Recombinant DNA Advisory Committee (RAC) and the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*. Both the role of the RAC and the depth and breadth of the *Guidelines* have changed in the last quarter of a century since their inception. The public and the scientific community have benefitted from NIH's oversight and stewardship. I am honored to appear before the subcommittee today to testify about the role of NIH in supporting gene transfer research and to describe to you our plans for the future.

Background

Since the advent of genetic engineering over 25 years ago, we have reaped many benefits from recombinant DNA technology. For example, recombinant DNA technology has made possible the manufacture of therapeutic proteins, such as human insulin and human growth hormone, which have widespread clinical application and benefit. Recombinant DNA technology, which has been integral in the sequencing of the human genome, also is being used to discern the genetic basis for many diseases and to design some of our most remarkable new treatments. Gene therapy is a relatively recent, and still experimental, application of recombinant DNA technology and it has caught the public's attention — not only because of its promise, but also because of the ethical and social implications of this research.

Clinical research, including human gene therapy research, is not without risk. Research is, by definition, experimental -- if the outcome were known, the study would not have to be conducted. Thus, the risks associated with the experimental treatment cannot always be predicted. For this reason, there exists a comprehensive system of Federal laws, regulations, and guidelines pertaining to the protection of human subjects in clinical trials. This fall, the tragic death of Jesse Gelsinger – a young man enrolled in a University of Pennsylvania clinical study for a disorder called partial ornithine transcarbamylase (OTC) deficiency – underscored the need for constant vigilance by researchers, by Federal agencies, and by Institutional Review Boards (IRBs) and Institutional Biosafety Committees (IBCs) responsible for the oversight and conduct of clinical gene therapy research. The NIH and the scientific community understand that the realization of the promise of clinical research in general, and gene transfer research in particular, is predicated on the public's trust – particularly the trust of the patients and families who volunteer to participate in clinical trials.

What is Gene Therapy and What is its Promise?

Gene therapy encompasses a variety of techniques directed toward therapeutic ends. For instance, gene therapy may be used to: 1) alter or supplement the function of a mutated gene by providing a copy of a normal gene; 2) directly alter and/or repair the mutated gene; or 3) provide a gene that adds missing functions or regulates the expression of other genes. The success of this technology is dependent upon not only the delivery of genetic material into the target cells, but

also the expression of the gene once it reaches its target site. Both of these requirements pose considerable technical challenges. With regard to gene delivery to target cells, a variety of "vectors" have been developed to serve this purpose. Most of these vectors are disabled viruses which work by delivering genes into certain human cell types, in much the same way as ordinary viruses infect cells.

Clinical gene transfer research has grown significantly since the first experiment in 1989. Interest in this arena of research, by both investigators and patients, has grown concomitantly with our increasing knowledge about disease-related genes. It's helpful to consider the scientific exploration of gene transfer as focused in two areas: methodologies for gene delivery and gene expression and specific diseases or conditions. Initially, gene transfer trials targeted either cancer, infectious diseases or single gene disorders such as cystic fibrosis. Increasingly however, the trend over recent years in gene transfer is to tackle diseases that involve more than one gene and are chronic. Prominent examples include heart disease, inadequate blood flow to the limbs, arthritis, and Alzheimer's. There has been increasing interest in the development of a broad array of vectors that investigators can choose from in order to best target the diseased cell type. Retroviruses can only infect actively dividing cell populations, which limits their usefulness in treating diseases of the heart or brain, where the cells are not actively dividing. There is also considerable and growing interest in the use of other methods apart from viral or bacterial vectors to deliver genetic material into cells. The use of small molecules composed of RNA and DNA to directly repair the defective DNA, rather replace the entire gene, has, for example, been applied in animal studies of sickle cell anemia.

To date, more than 4,000 patients have participated in gene therapy studies. Of the 372 clinical trials registered with the NIH, 89 percent are Phase I studies are designed to assess safety and toxicity. Ten percent are Phase II studies which assess safety and efficacy and generally involve a larger number and a more diverse population of patients. Only 1 percent of the trials (3 protocols) have progressed to Phase III efficacy studies. Thus, most human gene therapy clinical trials have been focused on safety, rather than efficacy. For this reason, it is perhaps more accurate to refer to this technology as "gene transfer," rather than "gene therapy, " until there is more evidence for the therapeutic benefit of this technology. NIH currently supports or conducts 157 gene transfer trials for a range of disorders, including cancer and AIDS.

Gene transfer research also has raised uniquely complex scientific, medical, ethical, and social issues that have warranted special oversight by the public and by the NIH, in particular. For example, the task of introducing genes into target cells carries with it the risk of inadvertent gene transfer to reproductive cells (sperm or egg cells), which could result in genetic changes being passed on to offspring. Similarly, because we can not yet fully control the placement and expression of the transferred genetic material, gene transfer may also pose unexpected health risks to the patient. And although the vectors used to transfer genes into cells are disabled viruses, these viruses may still retain some limited ability to cause disease, thus putting the patients and their close contacts at risk. Finally, this technology also could be put to controversial uses, e.g., for the enhancement of basic human traits such as height or hair color, rather than for

the treatment of disease.

NIH Oversight of Clinical Gene Transfer Research

The *NIH Guidelines* and the Recombinant DNA Advisory Committee (RAC), whose unique role in this class of research is defined in the *NIH Guidelines*, are the key tools by which the NIH oversees gene transfer research. Investigators conducting gene transfer research – either funded by the NIH or carried out at an institution that receives NIH support for recombinant DNA research of any type – are expected to comply with the *NIH Guidelines*. Failure to comply with the requirements set forth in the *NIH Guidelines* can result in the limitation, suspension or withdrawal of NIH support to the institution. NIH can also impose a requirement for prior NIH approval of any or all recombinant DNA projects at an institution. [All clinical gene transfer trials, regardless of funding source or research site, are also subject to Food and Drug Administration (FDA) regulations (21 CFR 312). The FDA has statutory authority to allow a gene transfer clinical study to proceed and, if necessary, to place a study on clinical hold in order to ensure the safety of human subjects.]

How did NIH come to play this unique role in this important arena of clinical research? In the early 1970s, scientists discovered a way to insert or recombine human and other species of DNA into bacterial genes, hence the term "recombinant DNA." This advance raised a number of serious concerns and questions among the public as well as the scientific community about the potential environmental, ecological, and infectious disease risks of this technology. Recognizing both the powerful benefits that might emerge from this research and the depth of public concern, the scientific community issued a self-imposed moratorium on recombinant DNA research and called for the formation of a national oversight body to ensure public discussion and oversight of this emerging technology. The RAC was subsequently established by the NIH and with its advice, NIH formulated the *NIH Guidelines*, which set forth policies and procedures designed to maximize the safety of basic recombinant DNA research.

In the 1980s, when it became increasingly apparent that recombinant DNA technology had the potential to lead to new gene-based treatments for human disease, the NIH established a subcommittee of the RAC to explore the scientific basis for and safety and ethics of so-called "gene therapy." Composed of scientists, ethicists, lawyers, and patient advocates, as well as liaison members from the FDA and the Office for the Protection from Research Risks (OPRR), among others, the subcommittee developed a new chapter in the *NIH Guidelines* (Appendix M). This new chapter delineated the roles and responsibilities of individual research investigators, NIH-funded institutions, IBCs, the RAC, the NIH Office of Recombinant DNA Activities (now known as the Office of Biotechnology Activities), and the NIH Director in the conduct of human gene transfer research. It also provided guidance for optimal design of preclinical and clinical research and standards for informed consent.

Implementation of the *NIH Guidelines*

The safe conduct of experiments involving recombinant DNA depends on the individual conducting such activities. In this regard, it is important to understand what the *NIH Guidelines* are and what they are not. The *NIH Guidelines* constitute an administrative framework in which safety is an essential and integral goal of research involving recombinant DNA molecules. The *NIH Guidelines* cannot anticipate every possible situation. The good judgment of the individuals conducting clinical research is the key essential to protection of human research subjects. The *NIH Guidelines* are intended to assist the Principal Investigator, the institution, the Institutional Biosafety Committee, the Biological Safety Officer, and the Institutional Review Board in determining safeguards that should be implemented. The *NIH Guidelines* will never be complete or final since all conceivable experiments involving recombinant DNA cannot be foreseen. Therefore, it is the responsibility of the institution and those associated with it to adhere to the intent of the *NIH Guidelines* as well as to its specifics. Each institution (and the Institutional Biosafety Committee acting on its behalf) is responsible for ensuring that all recombinant DNA research conducted at or sponsored by that institution is conducted in accord with the *NIH Guidelines.*

To this end, the *NIH Guidelines* require that all investigators governed by the *Guidelines* submit a copy of each human gene transfer protocol to the NIH. The *Guidelines* also delineate, among other things, the role of the RAC, the requirements for reporting of adverse events to the NIH, the role of the NIH in ensuring public access to information about human gene transfer trials, and the role of the Gene Therapy Policy Conferences.

The Role of the RAC

The RAC has several important roles in the oversight of gene transfer research -- both with regard to the *Guidelines* themselves and with regard to public review of protocols. In light of advances in the knowledge about the science and safety of gene transfer research, the RAC can recommend changes in the *NIH Guidelines* to the NIH Director. Proposed changes must be published in the *Federal Register* for public comment before any final change is made by the NIH Director. The RAC's most visible role is, however, the public review of gene transfer clinical protocols. This public review involves an in-depth discussion of the design of the protocol, preclinical safety data, the informed consent document, and any overarching scientific, safety or ethical issues relevant to the specific protocol.

During the first five years of human gene transfer research, there were many unanswered questions regarding the safety of this research. For this reason, every clinical gene transfer protocol registered with the NIH was required to undergo public RAC review and approval. Based on its review and discussion and any necessary follow-up with the principal investigators, the RAC recommended approval to the NIH Director, who then made a final decision as to whether the protocol could proceed.

By 1995, 149 protocols had been approved by the RAC and over 1,000 patients had been enrolled in worldwide trials. Many of the potential risks that initially raised public concern had

not materialized. In response to these advances in knowledge, the NIH instituted, on the RAC's recommendation, a new phase of oversight, by which only protocols deemed novel were subject to full public RAC review and approval. In making a determination whether an experiment is novel, and thus warranting full public RAC discussion, reviewers examine the scientific rationale, whether the preliminary in vitro and in vivo safety data were obtained in appropriate models and are sufficient, and whether questions related to relevant social and ethical issues have been resolved. Trials that did not present novel and/or unresolved issues were exempt from RAC review and approval and were forwarded directly to the FDA for its review.

In an effort to further expand and re-emphasize the unique role of the RAC in the public oversight of gene therapy research and, at the same time, cease RAC's duplication of the regulatory role of the FDA, in July 1996, the NIH Director proposed further changes to the role of the RAC. After careful consideration of public comment and consultations with a variety of constituency groups, including scientists, patients, and interested Members of Congress, the NIH Guidelines were revised in October 1997. Under the current NIH Guidelines, investigators are still required to submit a copy of the proposed research protocol to the NIH and to comply with all the policies and procedures, including adverse event reporting, outlined for the conduct of human gene transfer clinical research set forth in the NIH Guidelines; the RAC is still required to publicly review all novel protocols. However, the RAC no longer approves novel protocols. In addition, the RAC focuses more attention on much needed policy issues regarding the scientific basis for and safety and ethics of, emerging issues in gene therapy research, by convening Gene Therapy Policy Conferences.

Reporting of Adverse Events

A critical provision of the *NIH Guidelines* requires investigators to report immediately to the NIH any serious adverse event that occurs during the course of a gene therapy clinical trial. It is important to note that the requirement to submit adverse events to the NIH is not contingent upon whether the RAC does or does not have the authority to approve protocols. It is a requirement which has, in fact, remained unchanged in the *NIH Guidelines* since the advent of clinical gene transfer trials.

A serious adverse event is defined as any expected or unexpected adverse event related or unrelated to the intervention that results in any of the following outcomes: death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity or a congenital anomaly/birth defect, as well as important medical events that may require medical or surgical intervention to prevent one of those outcomes. In the context of a clinical trial, an adverse event can occur for many reasons and not all of these are related to the treatment, per se. In human gene transfer research, many of the patients enrolled in the trial already have serious and life-threatening diseases. Thus, a serious adverse event, or even a death, during the course of a clinical trial may be the result of the underlying disease, rather than the experimental treatment.

Although the FDA also requires reports of serious adverse events in human gene therapy, the timing and scope of these reports as well as the processes by which FDA responds to this information differ from those of the NIH. The NIH's unique role in the reporting of adverse events is perhaps best exemplified in the actions it took following notification of the death of Jesse Gelsinger. The investigators performing this trial reported the death to the NIH immediately, as required, and informed the NIH that they considered the cause of death to be directly related to the gene transfer. After consulting with the FDA and the RAC Chair, the NIH immediately notified the RAC, IBCs, OPRR, IRBs, and all principal investigators conducting gene transfer research. The NIH also requested additional data on a range of pre-clinical and clinical parameters from every registered researcher using adenoviral vectors in clinical trials – the vector used in the study in which Jesse Gelsinger participated. Adenoviral vectors are used in one quarter of the over 372 gene transfer trials registered with the NIH. A working group of the RAC was formed immediately to conduct an in-depth analysis of the data and, if necessary, to develop guidance regarding the continued use of adenoviral vectors in gene transfer studies.

This working group carried out a comprehensive review of the safety and toxicity data gathered from over 70 adenovirus-based clinical trials involving more than 1,200 research subjects and developed a number of preliminary recommendations. They recommended that human gene transfer research in which adenoviral vectors are being used should proceed, but with greater caution. In addition, the committee identified several other important needs, including the development of vector standards and the development of specific criteria for more uniform patient surveillance and monitoring. The working group emphasized the need for the RAC to convene more conferences which address the safety and toxicity of gene transfer, and which enhance the exchange of information among researchers. The RAC will consider the working group's final recommendations and develop a report of its conclusions and recommendations regarding the use of adenoviral vectors in human gene transfer research. As necessary, following a public comment process, the NIH will incorporate any recommendations into the *NIH Guidelines*.

Public Access to Data on Human Gene Transfer Research

One of NIH's primary responsibilities in its oversight in this arena is ensuring public access to data on gene transfer research. Recently, a number of questions have been raised about the status of the NIH gene transfer trial database, and thus, about whether the NIH was meeting its goal of making gene transfer trial data public. First and foremost, it is important to understand that data on all 372 human gene transfer trials registered with the NIH since the inception of the *NIH Guidelines* are now, and always have 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 and 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 any investigator or member of the public. In addition, the data reviewed at each RAC meeting are

posted on NIH's website (www.nih.gov/od/oba/). This includes discussion of any novel protocols, a list of the trials registered, and any reported serious adverse events. The website contains core information about each of the gene transfer protocols registered with the NIH – elements such as the protocol title, trial site, principal investigator, disease under study, and vector being used for the gene transfer. This information exists now and is widely available on NIH's website.

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 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 with regard to 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.

Gene Therapy Policy Conferences

Another important function of the RAC, which was instituted in October 1997, is the convening of Gene Therapy Policy Conferences (GTPCs). GTPCs provide a mechanism for in-depth exploration of emerging scientific and ethical issues raised by the continuing progress of the research. GTPCs have been held on three extremely complex issues – the ethical issues associated with the use of gene transfer technology for enhancement purposes, scientific and safety questions about the use of lentiviral vectors, and the scientific, medical, and ethical issues associated with prenatal gene transfer. GTPCs help inform the field, the RAC, and the public about emerging issues, and they can, and indeed have, yielded important consensus recommendations that guide the field.

Current Efforts to Ensure Appropriate NIH Oversight and Coordination with FDA

The NIH continues to consider new policies and procedures to appropriately ensure that its oversight of human gene transfer research is conducted efficiently and effectively. There is always need for improvement: the tragic death of Jesse Gelsinger and subsequent events have prompted a review of the role of the RAC and NIH in oversight of gene transfer research. In particular, recent events made it clear that the NIH needs to make some systemic changes to its oversight of adverse event reporting.

Re-evaluating NIH Oversight of Human Gene Transfer Research

In December 1999, the NIH Director established a working group of the Advisory Committee to the Director (ACD), 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 RAC and the *NIH Guidelines*. This charge was stimulated, in part, by growing concerns about the RAC's authority and its role with regard to protocol review.

In the recent past, as a result of differences between FDA's legislated requirement to review protocols within 30 days of submission to the Agency and the timing of quarterly RAC meetings, some novel clinical gene transfer trials have proceeded prior to public RAC review. This means that patients have been enrolled and treated prior to public RAC review. To this end, the ACD working group is being asked to recommend appropriate changes to the role and/or functions of RAC that would fully ensure that no patient is treated in a novel human gene transfer trial prior to public RAC review. The working group will consider options that have been put forth by the RAC, examine the merits of a return to RAC approval of all novel protocols, and/or propose another mechanism which would meet this goal.

The ACD working group is being asked to address three additional questions: 1) Are current NIH mechanisms adequate for coordination of its oversight of clinical gene transfer research with those of FDA, OPRR, IRBs, and IBCs, 2) Are additional NIH measures needed to minimize risk associated with clinical gene transfer research, and 3) What should the NIH role be with regard to reporting, analysis, and public discussion of serious adverse events. The working group will hold its first meeting this month and will meet again in March, in conjunction with the RAC, with the goal of submitting final recommendations to the Director, NIH, in May.

<u>Ensuring Compliance With the Reporting of Adverse Events</u>

The NIH's recent request to the gene transfer research community for data regarding the safety and toxicity of adenoviral mediated gene transfer revealed that many investigators governed by the *NIH Guidelines* have been under-reporting serious adverse events to the NIH. The adverse events that have been reported to us are quite varied both in the nature of the clinical events, as well as their cause. By and large, the events are due to progression of underlying disease, concomitantly administered drugs such as chemotherapy, or are known effects of some vectors, such as fever. We are deeply concerned about the under-reporting of serious adverse events to the NIH, and we are taking steps to better understand and to address this problem expeditiously.

The *NIH Guidelines* clearly place the responsibility for reporting all serious adverse events on the investigator and the institution. In addition, every investigator who registers a protocol with the NIH receives 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.

According to the *Guidelines*, as a result of non-compliance, the NIH can suspend, limit or terminate NIH funds for the gene transfer project or for all recombinant DNA research at an

institution. The NIH can choose 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 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 took 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 IRBs, IBCs, 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 NIH and 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 our ability 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 of 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, with 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 *Guidelines* are promulgated by the NIH, not by the RAC. Therefore, 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 any of the requirements set forth in the *NIH Guidelines*.

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Without clinical research, there can be virtually no new diagnostics, new treatments or new prevention strategies to improve the length and quality of our lives and the lives of our families. Gene transfer clinical research holds promise to treat or even prevent a wide variety of human diseases and conditions. It is incumbent upon investigators, funding institutions, and regulatory agencies to ensure that such research is conducted in as safe and ethical a manner as possible. If we are to improve the Nation's health through research, we must all work, in concert, to protect the most important participant in the research endeavor – the patient.

Mr. Chairman, this concludes my statement. The NIH appreciates the opportunity to participate in the Subcommittee's review of recent events in gene therapy research and the Federal role in overseeing this promising area of research. I would be pleased to answer any questions you may have.