

Regulatory Environment for Gene Transfer

Human gene transfer involves introducing a deoxyribonucleic acid (DNA) sequence into a human being, the incorporation of that DNA into the cells of the individual, and the expression of a functional gene "product" (such as a protein) by that DNA sequence. Transfer of the DNA sequence requires a "vector," meaning a mechanism by which the DNA sequence can be delivered to the proper location within the body. Typically, the delivery system is a "viral vector," which is a virus that has been modified to transfer the desired genetic material without, it is hoped, transferring viral genes that can cause illness.

Currently, gene transfer research efforts are focused on "gene therapy," meaning the delivery of genes to counteract genetic diseases, such as adenosine deaminase deficiency (ADA), cystic fibrosis, and cancer. The first attempt to treat a genetic disorder through gene transfer in the United States was performed on September 14, 1990 by researchers at the National Institutes of Health (NIH).¹ There are currently over 500 gene therapy "protocols," or experiments, registered with NIH.² All of these protocols are currently in an "investigational," or research, stage, and scientists continue to face significant hurdles in demonstrating the safety and effectiveness of gene therapy research.³ In addition, all of these protocols are limited to "somatic" gene transfer, meaning transfer of genes to the non-reproductive cells of the body. Some believe that in the future it may be possible to use gene transfer to modify the reproductive, or "germ," cells (sperm and egg) so that genetic traits may be passed on to future generations. Some also believe it will be possible in the future to use gene transfer to "enhance" traits such as intelligence and physical strength. Gene transfer therefore raises social and ethical, in addition to scientific, concerns. The death of a gene therapy research subject in 1999 has also led to heightened concern about the adequacy of federal oversight to protect human subjects participating in medical research.

Federal Oversight of Human Gene Transfer

Two agencies under the Department of Health and Human Services (DHHS), the NIH and the Food and Drug Administration (FDA), have oversight responsibilities for human gene transfer. Over time, the roles and responsibilities of these agencies has shifted in response to changing circumstances. This section briefly traces the history of oversight by these two entities and the current oversight functions played by each.

National Institutes of Health

Federal oversight of human gene transfer began well in advance of the approval of research into human gene therapy. On October 7, 1974, the NIH established the Recombinant DNA Advisory Committee (known as the RAC). The Committee was formed in response to public concerns relating to the safety of the newly discovered laboratory technique by which the DNA from different organisms could be recombined (termed "recombinant DNA").⁴ Initially, the RAC focused on safety concerns relating to the inadvertent release of recombinant DNA into the environment.⁵ In 1976 the RAC issued guidelines requiring institutions undertaking federally funded recombinant DNA research to establish an Institutional Biohazard Committee for local oversight of such research.⁶ These guidelines have been updated and modified over time.⁷

In 1980, concern shifted to the safety of introducing recombinant DNA into humans for therapeutic purposes. In that year, a researcher at the University of California at Los Angeles who was funded by the NIH conducted human gene therapy experiments abroad without the prior authorization of the university's institutional review board (IRB). In 1983, the RAC formed the Working Group on Human Gene Therapy, an interdisciplinary group comprising scientists, clinicians, lawyers, ethicists, policy experts, and a representative of the public. The Working Group recommended that the RAC broaden its scope to include review of protocols for human gene transfer. The Working Group also drafted over 100 questions relating to both science and ethics that scientists seeking to conduct gene therapy experiments in humans would be required to address in submissions to the RAC.⁸ The Working Group made the assumption that all consideration of such protocols would be public, and made no provision for the submission of proprietary information.

The RAC's initial requirements were developed significantly in advance of the conduct of the first gene therapy experiments. As gene therapy moved from the laboratory to the clinical stage, and more and more researchers, both academic and industry-based, sought to conduct gene therapy investigations in humans, concerns were raised regarding the burdensome and public nature of the RAC review process. In addition, as it became clear that FDA viewed itself as having a central regulatory role in the regulation of gene therapy, some viewed independent review of protocols by the RAC as unnecessarily duplicative. Others, however, feared that a reduction in RAC oversight would threaten the safety and public accountability of such research.⁹

Over time, the RAC has redefined its role regarding human gene therapy, and has moved from independent review and approval of individual gene therapy protocols to consideration of the ethical implications of new applications of human gene transfer. Gene therapy protocols that are funded by NIH or conducted at or sponsored by NIH-funded institutions

must be submitted to the RAC, and NIH maintains a registry of these protocols. Submission is voluntary for protocols that are funded solely with private funds and not conducted at or by an institution receiving NIH funding. RAC reviews registered protocols to determine if they raise unique and/or novel issues, and facilitates public discussion of such protocols. Issues requiring public discussion may include the use of new vectors or other gene delivery systems, application of gene therapy to new diseases, and other novel uses.¹⁰ For example, in 1997 NIH sponsored the first Gene Therapy Policy Conference to discuss the use of gene therapy for "enhancement," meaning for use in non-life-threatening conditions such as baldness.¹¹ The RAC has also stated that it "will not at present entertain proposals" for germline gene transfer experiments.¹² The RAC is widely seen as having a crucial role to play in providing a public forum for discussion and debate concerning the social and ethical issues raised by particular applications of human gene transfer.¹³

Food and Drug Administration

- [Federal Oversight of Human Gene Transfer](#)
- [State Oversight](#)

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Food and Drug Administration

From the early days of gene therapy research, FDA has consistently maintained that its existing statutory authority under the Food Drug and Cosmetic Act (FD&C Act) and Public Health Service Act (PHS Act) is sufficiently broad and flexible to encompass commercial applications of gene therapy. In 1984, FDA issued a policy statement declaring its intention to regulate gene therapy clinical trials, and contending that gene therapy was not a fundamentally different therapeutic modality that required increased scrutiny or new oversight mechanisms. According to the policy statement, "[n]ucleic acids used for human gene therapy trials will be subject to the same requirements as other biological drugs."¹⁴

Since 1984, FDA has communicated the regulatory requirements for these products through a series of informal and increasingly detailed guidance documents.¹⁵ In 1991, the Center for Biologics Evaluation and Research (CBER), the part of the agency overseeing gene therapy, issued a document informing manufacturers of the types of scientific issues and safety concerns that FDA believed were important to take into account in manufacturing and testing gene therapy products.¹⁶ An updated version of this document was issued in 1998.¹⁷

In 1993, FDA issued a guidance document explaining, for the first time, the legal basis for its regulation of gene therapy. The document reiterated that existing FDA statutory authorities, "although enacted prior to the advent of . . . gene therapies, are sufficiently broad in scope to encompass these new products and require that areas such as quality control, safety, potency, and efficacy be thoroughly addressed prior to marketing."¹⁸ The document defined gene therapy as "a medical intervention based on modification of the genetic material of living cells."¹⁹ Such cells "may be modified ex vivo for subsequent administration or may be altered in vivo by gene therapy products given directly to the subject."²⁰ The genetic manipulation "may be intended to prevent, treat, cure, diagnose, or mitigate disease or injuries in humans."²¹ According to the document, "[f]inal products containing the genetic material intended for gene therapy are regulated as biological products . . . or as drugs"²² In other words, the regulated "products" of gene therapy are the DNA that is administered to the patient and the delivery system (e.g., viral vector) used to transport that DNA. As such, they require the premarket submission of an application, and approval of such application by FDA, before they may be distributed in interstate commerce.

FDA oversight of gene therapy begins at the point in which a researcher wants to test the product in a human being. As with any unapproved product, the researcher must first submit an "investigational new

drug" (IND) application to FDA demonstrating that the available preclinical (e.g., animal or laboratory) data justify administering the product to a human to see if it is safe and effective. The IND rules also require that the researcher has obtained approval from an institutional review board (IRB). Since the death of Jesse Gelsinger, a gene therapy research subject, in 1999, FDA, together with NIH, has announced new initiatives to protect participants in gene therapy trials,²³ and FDA has suspended gene therapy trials at institutions the agency has found in violation of FDA requirements.²⁴

FDA has not yet approved for sale any human gene therapy product. Currently, FDA is overseeing approximately 210 active IND gene therapy studies.²⁵

State Oversight

No states have laws regulating gene therapy. However, research subjects who believe they have been injured as a result of gene therapy experiments may use state or common law principles of general applicability (e.g., negligence) to bring lawsuits in state or federal court against the researchers, institutions, and others involved in the research. Courts may therefore be placed in the position of evaluating the adequacy of the conduct of gene therapy research. Thus far, no court has issued an opinion addressing the conduct of gene therapy research.

¹ Jeff Lyon, Peter Goner, *Altered Fates* 227-240 (1996).

² See NIH, Office of Biotechnology Activities, [Human Gene Transfer Protocols](#).

³ See Larry Thompson, [Human Gene Therapy: Harsh Lessons, High Hopes](#), FDA Consumer (2000).

⁴ Judith E. Beach, *The New RAC: Restructuring of the National Institutes of Health Recombinant DNA Advisory Committee*, 54 *Food Drug L. J.* 49 (1999).

⁵ Richard A. Merrill, Gail H. Javitt, *Gene Therapy, Law and FDA Role in Regulation*, in *Encyclopedia of Ethical, Legal, and Policy Issues in Biotechnology* 321 (Thomas J. Murray and Maxwell J. Mehlman, eds. 2000)

⁶ 41 Fed. Reg. 27902 (July 7, 1976).

⁷ See Joseph M. Rainsbury, *Biotechnology on the RAC – FDA/NIH Regulation of Human Gene Therapy*, 55 *Food Drug L. J.* 575, 576 n. 9 (2000) (citing current guidelines).

⁸ *Id.* at 581.

⁹ See Merrill and Javitt, *supra* note 5, at 323-329.

¹⁰ NIH, Recombinant DNA Advisory Committee, [Recombinant DNA and Gene Transfer](#).

¹¹ 62 Fed. Reg. 44386 (Aug. 20, 1997) (notice of meeting).

¹² See NIH, [Guidelines for Research Involving Recombinant DNA Molecules](#), Appendix M, at 94.

¹³ Merrill and Javitt, *supra* note 5, at 333 (quoting Dr. Philip Noguchi).

¹⁴ 49 Fed. Reg. 50878 (1984).

¹⁵ For a list of these documents and related materials, see [FDA's website](#).

¹⁶ 56 Fed. Reg. 61022 (1991). ¹⁷ [Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy](#) (1998).

¹⁸ *Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products*, 58 Fed. Reg. 53248 (Oct. 14, 1993).

¹⁹ *Id.* at 53251.

²⁰ *Id.*

²¹ *Id.*

²² *Id.*

²³ HHS News, *New Initiatives to Protect Participants in Gene Therapy Trials* (Mar. 7, 2000) (press release)

²⁴ See Thompson, *supra* note 2.

²⁵ Center for Biologics Evaluation and Research, [Human Gene Therapy and the Role of the Food and Drug Administration](#) (2000).

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