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Light, Fast, and Flexible: A New Approach to Regulation of Human Gene Therapy

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> "I have read that my son's death has been called by one of the leaders in this field as a pothole on the road to gene therapy. His death was no pothole. It was an avoidable tragedy from which I will never fully recover."[1]

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I. INTRODUCTION

The subject of human gene therapy conjures up different images for different people, from visions of a cure for all human illness,[2] to a superior, genetically enhanced race of humans, as in the movie "Gattaca."[3] No one yet knows what the reality will turn out to be. However, one thing is clear: the potential for human gene therapy to make a difference in our lives is tremendous. Gene therapy is one part of the biotechnology revolution that may open doors heretofore closed to patients, doctors, and researchers for the treatment of disease. Along with its potential to cause change, human gene therapy presents many new challenges. This Article introduces some of the scientific and legal issues surrounding this promising field of treatment.

Specifically, Part II of this Article describes the current state of the science of human gene therapy and the problems facing the industry today. Human gene therapy consists of introducing a functioning gene into the somatic cells[4] of a patient in order to correct an inborn genetic error or to provide the cells with a new gene function.[5] Although a physician may have several methods to treat patients undergoing gene therapy, all currently present the researchers with interesting concerns, such as exactly how to get a correctly functioning gene into a patient's cell in order to provide a functioning copy of that patient's defective gene. As for the industry of gene therapy, although the science is older, the clinical field of human

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2. A middle ground is the case of Ashanti DeSilva, a young girl with a lethal hereditary disease that prevented her immune system from operating, resulting in repeated, severe infections. She was the first patient to undergo federally approved gene therapy treatments. With the aid of the continuing treatments, her immune system began to function normally, allowing her for the first time to begin a normal, active life. *See* W. French Anderson, M.D., *Gene Therapy*, SCI. AM. 124, 124 (Sept. 1995).

3. A 1997 movie set in a world where a super-race of genetically engineered humans formed an elite class of people and all people with average intelligence or bad hair or poor vision were inferior and thus relegated to menial jobs. GATTACA (Columbia TriStar 1997). While this is an example of gene enhancement, and therefore outside of the scope of this article, much of the public makes no distinction between gene therapy and gene enhancement.

4. Generally speaking, somatic cells are all body cells except for reproductive cells, i.e., egg and sperm cells, which are called "germ cells." *See* BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 1012 (3rd ed. 1994).

5. *Gene Therapy: Status, Prospects For the Future, and Government Policy Implications: Hearing Before the U.S. House of Representatives Comm. on Science, Space, and Technology*, 103rd Cong. 25 (1994) [hereinafter *House Hearings*, Dr. Wivel testimony] (written testimony of Dr. Nelson A. Wivel, Director, Office of Recombinant DNA Activities, NIH). Dr. Verma, of the Salk Institute, described the goal of gene therapy: "[Gene therapy's] product[s] should have the ability to either cure the disease, ameliorate the disease or perhaps slow down the progression of the disease."*Gene Therapy: Is There Oversight for Patient Safety: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions*, 106th Cong. 60 (2000) [hereinafter *Senate Hearings*, Dr. Verma testimony] (statement of Inder Verma, Ph.D., Salk Institute). For an informative website concerning gene therapy, written for those with some background in molecular biology, see <http://www.mc.vanderbilt.edu/grcr/gene>.

gene therapy is only about ten years old.[6] Although early promise led to substantial investment in gene therapy research, many companies are rethinking their investment in gene therapy research because of trouble with the science and the lack of any marketable products.[7]

Part III of this Article chronicles the current state of the law regarding gene therapy, both federal regulatory law and tort law, and the resulting problems for all of the participants. For the past ten years, federal regulation of gene therapy has principally involved two federal agencies, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH).[8] Rather than rushing to create new regulations and agencies, existing agencies have tried to fit the new gene therapy technologies into their established regulatory framework and have adopted a "wait and see" policy to determine how this approach will work.[9] The FDA regulates gene therapy as it would a new drug.[10] It approves protocols submitted by researchers and monitors the results of the protocols, including patients' adverse reactions during and after the therapy.[11] The NIH provides federal grant money to qualified researchers who are studying gene therapy.[12] Through its Recombinant DNA Advisory Committee (RAC), the NIH approves novel protocols and monitors the protocols and adverse reactions for researchers using NIH grant money.[13] There is significant overlap in the regulatory duties of both agencies, resulting in a confusing duplication of reporting requirements for researchers.

In addition to federal agency regulations, there are tort laws that apply to human gene therapy. Two such areas are the tort law theories of informed consent and strict product liability.[14] Under an informed consent cause of action, a patient can sue a doctor and his or her employer if he or she does not provide to the patient sufficient material information to allow the patient to make an informed decision whether to undergo gene therapy.[15] With strict product liability, the product manufacturer

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6. *Gene Therapy: Status, Prospects For the Future, and Government Policy Implications: Hearing Before the U.S. House of Representatives Comm. on Science, Space, and Technology*, 103rd Cong. 39 (1994) (statement of Phillip Noguchi, M.D., Director, Division of Cellular and Gene Therapies, Office of Therapeutics, FDA).

7. *See infra* Part II.B. and accompanying text.

8. *See infra* Part III. Although the NIH has no statutory authority to regulate, the penalty clause in the NIH Guidelines § IV.D acts to provide a type of de facto regulatory power. *See infra* note 105 and accompanying text. For the purposes of this article, the NIH's de facto power will be referred to as regulatory power.

9. Martha J. Carter, *The Ability of Current Biologics Law to Accommodate Emerging Technologies*, 51 FOOD & DRUG L.J. 375, 376 (1996).

10. *See* David A. Kessler et al., *Regulation of Somatic-Cell Therapy and Gene Therapy by the Food and Drug Administration*, 329 NEW ENG. J. MED. 1169, 1169 (Oct. 14, 1993).

11. *See infra* notes 177-80 and accompanying text (describing the FDA's monitoring responsibilities).

12. *See generally* Gregory A. Jaffe, *Inadequacies in the Federal Regulation of Biotechnology*, 11 HARV. ENVTL. L. REV. 491(1987).

13. *See infra* Part III.A.

14. *See infra* Part III.A.2.

15. *See* JOHN L. DIAMOND ET AL., UNDERSTANDING TORTS 103 (1996). The employer would be liable under the theory of respondeat superior, because the physician would be an employee and acting within the scope of his employment. *Id.* at 221.

would be strictly liable in tort for a defective gene therapy product that causes injury to the consumer.[16] Some commentators suggest that biotechnology is a strategic industry and ought to be protected from some of the burden of strict product liability.[17]

After more than ten years of this experimental system of regulation, the system shows serious problems, as described in Part III B. There are challenges for all of the participants in human gene therapy, including the public, the regulating agencies, the gene therapy companies, and researchers. The public is concerned about the issues of patient safety, informed consent, and the protection of confidential patient information.[18] The regulating agencies have problems with researchers' noncompliance with reporting requirements for adverse events, oversight of the informed consent process, lack of agency resources to cope with policing a rapidly changing science, and interagency rivalry given the overlap in regulatory requirements.[19] The gene therapy companies worry about duplicative and conflicting reporting requirements by the FDA and the NIH, and preventing proprietary information from becoming publically available.[20]

Part IV of this Article briefly discusses five changes to the current regulatory structure which may help alleviate some of the problems created by human gene therapy. First, the Senate should establish a standing subcommittee under the Senate Committee on Health, Education, Labor, and Pensions in order to involve Congress in monitoring regulation of this important industry. Second, the RAC should be moved under the direct control of the office of the Secretary for Health and Human Services, and its directives should be made binding on both the NIH and the FDA. Third, the Department of Health and Human Services should increase the FDA's budget to enable it to effectively regulate gene therapy clinical trials and product manufacturing with personnel who are knowledgeable about gene therapy. Fourth, the FDA should mandate the appointment of independent patient advocates to explain to potential gene therapy clinical trial patients the risks and benefits of treatment and to ensure that the physician-researchers are adequately disclosing all of the risks to the patient. The final proposal is that Congress act to prohibit strict products liability for design defects in human gene therapy products. What this Article proposes is a regulatory framework that is light, fast, and flexible where necessary.[21]

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16. RESTATEMENT (SECOND) OF TORTS § 402A (1965).
17. *See infra* note 152 and accompanying text.
18. *See infra* Part III.B.
19. *Id.*
20. *Id.*
21. Light, as in limiting the number of participants to avoid becoming an unwieldy bureaucracy; fast, to keep up with the rapidly changing science, and flexible, to be able to adapt itself if one approach does not work.

II. CURRENT STATE OF THE SCIENCE—PROBLEMS IN THE INDUSTRY

Clinical trials involving human gene therapy began about ten years ago.[22] There are currently several methods whereby a scientist can introduce a functional gene into a cell that contains a non-functioning gene copy. There are several problems common to all of the current gene therapy techniques. In addition, as is normal with high technology industries, there have been snags with turning vision into reality. Venture capitalists and large pharmaceutical companies tire of waiting for marketable products; at the same time, researchers admit to at least one death directly attributable to gene therapy.

A. Current State of the Science

Human gene therapy consists of introducing a functioning gene into the somatic cells of a patient in order to correct an inborn genetic error or to provide a cell with a new function.[23] Today it is only feasible to correct diseases controlled by a single gene, such as cystic fibrosis.[24] Gene therapy commonly relies on the use of a vector[25] to put the functional gene into the host cell that contains a defective gene. To date, the most effective vectors have been modified viruses, such as adenoviruses and retroviruses.[26] In order to make the viral vector non-pathogenic to humans, scientists remove much of the virus's own genetic material, leaving only the segments necessary for the virus to successfully insert its "payload" of the functional gene into the host cell.[27] There are three methods whereby a physician or scientist can insert a correct gene copy into a cell that contains a defective gene: ex vivo therapy; in situ therapy; and in vivo therapy.

In ex vivo gene therapy, the scientist removes living cells containing the defective gene from the patient, uses a vector to insert a correct copy of the gene into the cell, and returns the cell to the patient's body.[28] Researchers have used this treatment for blood disorders such as hemophilia. One dilemma with this type of

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22. *Supra* note 6 and accompanying text.

23. *See House Hearings*, Dr. Wivel testimony, *supra* note 5, at 25; *Senate Hearings*, Dr. Verma testimony, *supra* note 5, at 62.

24. *See House Hearings*, Dr. Wivel testimony, *supra* note 5, at 20 (pointing out that there are ten protocols approved for cystic fibrosis).

25. A vector is merely a vessel or agent used to carry the desired piece of DNA to the patient's cell, "dock" with and be taken in by the cell. *See* ALBERTS, *supra* note 4, at G-23.

26. *See* Anderson, *supra* note 2, at 124. Adenoviruses cause the common cold. Today, about 25-30% of the vectors that researchers use in gene therapy are adenoviruses. *Senate Hearings*, Dr. Verma testimony, *supra* note 5, at 63 (describing three principal types of vectors for gene therapy, retroviral vectors, adenoviral vectors, and AAB vectors. Retroviral vectors work very well to introduce genes and get long term results, but only work with cells that are dividing, such as cancer cells. Adnenoviral vectors generally produce shorter term results, but can enter non-dividing cells.).

27. *See* Anderson, *supra* note 2.

28. *Id.* at 126.

treatment is that most cells have limited life-spans,[29] so the treated cells naturally die over time and must be replaced with additional treated cells in order to prevent the disease from recurring.[30]

In situ therapy differs from ex vivo therapy in that the patient's cells are not removed from his or her body before treatment, but instead are treated "in position."[31] In this therapy, the scientist uses a vector containing the correct gene and injects the vector directly into the target tissue in the patient's body.[32] The vector carries the functional gene into the cells of the target tissue where they may insert into the cell's DNA, thus providing a correct copy of the gene for that cell. Examples of the use of this method are in the treatment of cystic fibrosis and muscular dystrophy.[33] This type of therapy works best with localized conditions such as cystic fibrosis, but is not effective for systemic genetic disorders.

The last type of therapy is in vivo therapy. In vivo therapy ideally uses a vector chosen or engineered to bind to and enter only its target cell type, such as only liver cells, while bypassing all other cell types.[34] In this type of therapy, the scientist injects the vector into the patient's bloodstream, where it is carried throughout the body but only enters the target cells, thus potentially introducing a correct gene into, for example, all of the body's liver cells.[35] The advantages to this type of therapy over ex vivo therapy are that it is less expensive,[36] and it can treat more cells. In vivo therapy has the greatest potential for large-scale use because the therapy need not be individually tailored to the patient, and it can be used for treating systemic diseases.[37] However, there are several problems with this type of therapy. The first obstacle is that researchers have had trouble engineering vectors that can evade the body's immune responses long enough to reach the target cells.[38] Second, there has been difficulty engineering a vector that can efficiently insert its gene "payload" into the target cell.[39]

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29. For example, red blood cells (erythrocytes) live only 120 days before the body replaces them. *See* ALBERTS, *supra* note 4, at 1169.

30. *See* Anderson, *supra* note 2, at 127.

31. *Id.*

32. *Id.*

33. *Id.*

34. *Id.*

35. *Id.*

36. In this type of therapy, the patient's cells do not need to be removed, kept alive in the laboratory until successfully treated, and then reintroduced into the patient. The treatment, once developed, will be more of an off-the-shelf product than an individually tailored product.

37. *See* Anderson, *supra* note 2, at 127.

38. Paul N. Reynolds & David T. Curiel, *Strategies to Adapt Adenoviral Vectors for Gene Therapy Applications: Targeting and Integration,* THE DEVELOPMENT OF HUMAN GENE THERAPY 111, 111 (Theodore Friedmann ed., 1999). Because some of the most efficient vectors are viruses, they may trigger the host body's immune system, just as when you catch a cold. If the vector triggers the body's immune system, the patient may suffer a systemic inflammatory response, which is potentially fatal to the patient. *See* Eliot Marshall, *Gene Therapy Death Prompts Review of Adenovirus Vector,* 286 SCIENCE 2244, 2244 (Dec. 17,1999).

39. *See* Anderson, *supra* note 2, at 127.

Additionally, there are several concerns common to all types of gene therapy. First, the gene may fail to insert into the host's DNA at all or it may insert incorrectly and function ineffectively.[40] When this happens, the corrected gene is in the cell but simply cannot function well enough to make a difference in the patient's disease. More dangerous to the patient is the fact that the correct copy of the gene may insert into a cancer-suppressing gene, thereby disrupting that gene's function.[41] As a result, the treatment may trigger the cell to become cancerous.[42] Moreover, there is a small chance that the vector may travel through the blood stream to the reproductive organs and insert in the germ line cells, potentially creating birth defects.[43] Finally, as the successfully treated cells age and die, there may be too few cells remaining with the corrected gene to prevent the disease from recurring, thus entailing a new round of treatment. As a result of some of these concerns with the science of gene therapy, the gene therapy industry has not been as successful in treating human ailments.

B. Trouble in the Gene Therapy Industry

Despite the dazzling promise that the future of gene therapy seems to hold, there is a dark side to this emerging science. For example, in September 1999, Jesse Gelsinger died of a systemic inflammatory response four days after doctors in a clinical trial injected him with an adenovirus vector that contained a gene to produce an essential liver enzyme.[44] As a result, on January 19, 2000, the FDA halted all seven of the clinical trials that the University of Pennsylvania's Institute for Human Gene Therapy had been conducting.[45] The FDA halted the clinical trials after finding "serious deficiencies" in the way the Institute was monitoring its trials.[46] Because the Institute is possibly the most respected and best-funded center for public research in human gene therapy,[47] the problems that the FDA found there may be more pervasive at other research institutions. As of the date of this Article, the FDA

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40. THEODORE FRIEDMANN, M.D., GENE THERAPY-FACT AND FICTION IN BIOLOGY'S NEW APPROACHES TO DISEASE 101 (1994).

41. *See* Anderson, *supra* note 2, at 127.

42. *See House Hearings*, Dr. Wivel testimony, *supra* note 5, at 33. Although scientists have made great strides in mapping the human genome and identifying transcription promoter sequences for individual genes, there is currently no mechanism for controlling where the introduced gene will insert in the mammalian host cell's DNA. *See* FRIEDMANN, *supra* note 40, at 99.

43. This is called "inadvertent germ line transfer." *Gene Therapy: Status, Prospects For the Future, and Government Policy Implications: Hearing Before the U.S. House of Representatives Comm. on Science, Space, and Technology*, 103rd Cong. 122 (1994) [hereinafter *House Hearings*, Dr. Abbott testimony] (statement of Robert T. Abbott, President and CEO of Viagene, Inc.). If the gene inserts into the human equivalent of the hox gene, which controls when and where the fetus' limbs develop, it would result in severe and possibly bizarre birth defects. *See* SCOTT F. GILBERT, DEVELOPMENTAL BIOLOGY 629-30 (4th ed. 1994).

44. *See* Marshall, *supra* note 38. The gene was for the liver enzyme ornithine-transcarbamylase. *Id.*

45. *See* Eliot Marshall, *FDA Halts All Gene Therapy Trials at Penn*, 287 SCIENCE 565, 565 (Jan. 28, 2000).

46. *See Id.* (quoting an eight page FDA report of preliminary observations regarding the Institute).

47. *Id.*

and the research institutions have halted more than a dozen other gene therapy trials.[48] Recently, researchers reported one additional death in Florida that may have also been caused by gene therapy.[49]

Even before Jesse Gelsinger's death, private companies have been quietly backing away from their investments in gene therapy.[50] In 1995, there were fourteen biotechnology firms sponsoring gene therapy trials; today, half of those companies no longer exist as independent companies.[51] In 1998, the Swiss drug firm Novartis discontinued research into its heralded gene therapy project for brain tumors.[52] The following year, the biotechnology "powerhouse" Chiron almost eliminated new gene therapy research conducted in-house.[53] Dr. Inder Verma, of the Salk Institute, said at a recent biotechnology conference that gene therapy's successes to date have been almost nonexistent.[54] While there still remain some forty to fifty companies with some involvement in gene therapy, it appears that the human gene therapy industry is at a critical decision-making point: to go forward or to abandon current research projects and divert scarce resources into other, more immediately profitable, research.[55]

To date there are no gene therapy products on the market.[56] Market analysts predict that the first gene therapy products will enter the market in 2003.[57] The closest candidate appears to be a treatment for hemophilia.[58] There are about 17,000 hemophiliacs in the United States who treat their uncontrolled bleeding with injections of blood clotting factors, at a cost of about $1,000 per injection.[59] If gene therapy works for these people, they will be able to produce their own clotting factors, thus eliminating the need for the costly injections and improving the quality of their life and health.

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48. Michael McCarthy, *U.S. Tightens Oversight of Gene-Therapy Trials*, 355 LANCET 997, 997 (2000).

49. Charles W. Henderson, *Gene Therapy Panel Deadlocks*, GENE THERAPY WKLY., Mar. 23, 2000, *available in* 2000 WL 11696002.

50. *See* Marshall, *supra* note 38 (stating that the field of gene therapy was "struggling to live up to the promise and hype surrounding the first gene therapy trials a decade ago."); Ken Garber, *High Stakes for Gene Therapy*, TECH. 58, 58 (March-April 2000). Conversely, stock in companies doing research into the human genome has surged in price, often as a result of potential and possibly evanescent intellectual property rights revenues. *Id.*

51. *See* Garber, *supra* note 50, at 58.

52. *Id.*

53. *Id.*

54. *Id.* at 59. However, this does not imply that there are no near successes. *See Senate Hearings*, Dr. Verma testimony, *supra* note 5, at 59 (describing several anecdotal examples, i.e., as yet unpublished stories, of success in hemophiliac and cancer gene therapy patients).

55. Jim Papanikolaw, *Waiting for the Fruits of Gene Therapy*, 257 CHEM. MARKET REP. 15 (Mar. 20, 2000) (listing multiple examples of companies researching gene therapy). The formation rate of new pharmaceutical-gene therapy partnerships is stagnant. *Id.* at 16.

56. *Id.*

57. *Id.*

58. *See* Garber, *supra* note 50, at 60 (chronicling the race among several biotechnology firms to be the first with a gene replacement therapy for hemophilia).

59. *Id.*

Yet, in spite of these somber moments in the history of human gene therapy, and the lack of any current products, the promise that gene therapy holds is alluring. Current clinical trials promise the hope of treating HIV,[60] breast cancer,[61] hemophilia,[62] cardiovascular disease,[63] and cystic fibrosis.[64] One industry consulting company forecasts that sales resulting from gene therapy will hit $4.7 billion by 2008.[65] Considering all of the possible gene-related diseases, including genes that fail with age, gene therapy is potentially relevant to virtually everyone.[66]

To summarize, while the science of gene therapy promises wonders, it is still only a rapidly changing infant science at this stage. Human gene therapy continues to raise new safety and ethical issues that the law must address.

III. CURRENT STATE OF THE LAW—TROUBLES WITH THE CURRENT REGULATORY SYSTEM

There are two levels of law that apply to human gene therapy. The first level is federal statutory and agency regulatory law, which controls clinical trials and product manufacturing. Under federal regulatory law, coupled with the NIH's control of clinical trials via NIH funding, the FDA and the NIH have a sort of overlapping jurisdiction to regulate human gene therapy clinical trials. This jurisdictional overlap results in confusing and duplicative reporting requirements for researchers, and concerns about access to proprietary trade secrets and confidential patient information. Underneath federal regulatory law lies the second level, the ever present issue of tort law liability for the industry and researchers.

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60. *See generally* CLAY SMITH, M.D., GENE THERAPY FOR HIV INFECTION (1998).

61. *Gene Therapy: Status, Prospects For the Future, and Government Policy Implications: Hearing Before the U.S. House of Representatives Comm. on Science, Space, and Technology*, 103rd Cong. 16 (1994) [hereinafter *House Hearings*, Dr. Greenwood testimony] (statement of Dr. M.R.C. Greenwood, Associate Director for the Science Office of Science and Technology Policy) (explaining that some breast cancer is the result of single gene susceptibility).

62. *See* Garber, *supra* note 50.

63. *See Senate Hearings*, Dr. Verma testimony, *supra* note 5, at 60 (mentioning gene therapy for angiogenesis).

64. *Gene Therapy: Is There Oversight for Patient Safety: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions*, 106th Cong. 11 (2000) [hereinafter *Senate Hearings*, Kast testimony] (statement of Eric Kast, cystic fibrosis gene therapy clinical trial participant).

65. *See* Papanikolaw, *supra* note 55 (quoting Front Line Strategic Management Consulting, a Foster City, California based company).

66. *See House Hearings*, Dr. Greenwood testimony, *supra* note 61, at 8.

A. Current State of the Law

1. Federal Regulation

To date, Congress has been generally silent on the topic of gene therapy regulation.[67] Early on, federal agencies responded cautiously to the new industry, reasoning that using existing health and safety laws would provide more immediate protection and certainty for the industry than would enacting new legislation.[68] In 1986, the Office of Science and Technology Policy, a presidential advisory council, announced a "Coordinated Framework for Regulation of Biotechnology" (Coordinated Framework).[69] The Coordinated Framework examined a proposed interface of several federal agencies to regulate, among other biotechnology subjects, human gene therapy.[70] The Coordinated Framework emphasized the significant expertise of each of the federal agencies in dealing with living organisms, their manufacture, and their ultimate use, including their release into the environment.[71] In essence, it counseled a wait-and-see approach to regulating biotechnology. The primary agencies involved with regulating human gene therapy are the FDA and the NIH.

a. The FDA

The FDA is organized under the Department of Health and Human Services.[72] The FDA's mission is to promote public health by reviewing and regulating clinical research and regulating the marketing of products under its purview.[73] Such products include drugs, biologics, food, food additives, medical devices, and animal drugs, all under the authority of the Federal Food, Drug and Cosmetics Act (FFDCA)[74] and the Public Health Service Act (PHSA).[75]

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67. At one point before the NIH established the RAC in the early 1970's, there were sixteen pieces of proposed legislation in Congress for regulation of recombinant DNA research. None passed. Nelson A. Wivel & W. French Anderson, *Human Gene Therapy: Public Policy and Regulatory Issues*, *in* THE DEVELOPMENT OF HUMAN GENE THERAPY 671, 674 (Theodore Friedmann ed., 1999). The House Committee on Science, Space and Technology held a hearing on the subject of gene therapy in 1994. *See Gene Therapy: Status, Prospects For the Future, and Government Policy Implications: Hearing Before the U.S. House of Representatives Comm. on Science, Space, and Technology*, 103rd Cong. (1994).

68. Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302, 23,303 (1986).

69. *Id.* at 23,302.

70. *Id.*

71. *Id.* at 23,303.

72. *See* Jaffe, *supra* note 12, at 517.

73. 21 U.S.C.A. § 393(b) (West 1999).

74. 21 U.S.C.A. §§ 301-392 (West 1999 & Supp. 2000).

75. 42 U.S.C.A. § 262 (West 1999).

Gene therapy products based on viral vectors meet the statutory definition of biologic products,[76] and are therefore subject to FDA regulation.[77] Moreover, the FDA has interpreted the definition of the word "drug" in the FFDCA to include the products of somatic cell manipulation.[78] According to FDA officials, gene therapy may involve two types of processes.[79] As defined by the FDA, gene therapy includes interventions wherein the patient's genetic material is deliberately altered in order to prevent or treat disease.[80] In addition, gene therapy may involve somatic cell manipulation wherein cells from humans or animals are manipulated to change their biological characteristics and are then introduced into the patient's body.[81] According to FDA officials, if researchers treat cells ex vivo to expand their number, select certain cells, or add pharmacological agents, this is a manufacturing step subject to FDA regulation.[82]

The FDA has not proposed any new FDA review office or new requirements for biotechnology, stating that its current procedures were adequate for regulating biotechnology products.[83] It dispersed oversight of biotechnology products to existing offices and added scientific expertise as necessary to deal with the new technology.[84] Within the FDA, the Office of Therapeutics Research and Review (Office of Therapeutics) oversees all activities regarding gene therapy research.[85] The FDA also published several documents, called "Points to Consider," that describe issues that manufacturers "might wish to consider" in their research and production of gene therapy products.[86]

The FDA requires that researchers performing human gene therapy clinical studies file an Investigational New Drug application (IND).[87] The IND application must contain product manufacturing and testing information to permit the FDA to protect patients in the trial from being exposed to significant and unreasonable

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76. The PHSA defines "biological product" to include "any virus . . .blood, blood component or derivative . . .applicable to the prevention, treatment, or cure of diseases or condition of human beings." 42 U.S.C. § 262 (i) (West Supp. 2000).

77. *Id.*

78. *See* Kessler, *supra* note 10.

79. *Id.*

80. *Id.*

81. Somatic-cell therapy is "the administration to humans of autologous [cells from that patient's body], allogeneic [cells from another human body], or xenogeneic [cells from an animal's body] living somatic cells that have been manipulated or processed to change their biologic characteristics." *Id.* Generally speaking, somatic cells are all body cells other than reproductive cells such as egg and sperm cells, called "germ cells." *See* ALBERTS, *supra* note 4.

82. *See* ALBERTS, *supra* note 4.

83. 49 Fed. Reg. 50,878 (1984).

84. *See* Carter, *supra* note 9, at 376.

85. *Gene Therapy: Is There Oversight for Patient Safety: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions,* 106th Cong. 39 (2000) [hereinafter *Senate Hearings,* Dr. Siegel testimony] (statement of Dr. J.P. Siegel, Director, Office of Therapeutics, FDA). Only about 20% of the active trials overseen by the Office of Therapeutics are gene therapy trials. *Id.* at 46.

86. 49 Fed. Reg. 50, 879 (1984).

87. *See* Kessler, *supra* note 10, at 1169.

risk.[88] This researcher-supplied information often contains proprietary information and confidential patient information.[89] Both the research institution and the patients are protected from public disclosure of this information because the FDA is bound by regulations on confidentiality and may only release information on the sponsor, the title and the indication.[90] This statutory limitation protects proprietary trade secret information that is especially important to private companies.

The FDA performs the majority of its inspections at the time of the protocol approval "to ensure that the data in the application are what they purport to be."[91] The FDA does not routinely conduct a physical investigation of the clinical trial while it is proceeding, though it communicates with the Principal Investigator (PI)[92] regarding how to handle the protocol as the trial proceeds, and how to deal with adverse events.[93] Although the FDA does not physically inspect all of the gene therapy clinical trials,[94] in March 2000, the FDA tightened its regulations by requiring that a PI appoint someone who is not directly involved with the PI's clinical trial to monitor patient safety by conducting random, surprise inspections.[95]

Once a gene therapy or somatic cell therapy achieves success in clinical trials, qualified manufacturers who hold FDA licenses both for the specific product and for the manufacturing facilities specific for that product, may commercially manufacture the product.[96] A manufacturer must include detailed information in its license application regarding manufacturing processes, product and labeling specifications, summaries of relevant preclinical data, and analyses of the design, conduct, and results of the clinical trials.[97] Most of the FDA's resources for inspection are reserved for when a product comes to market.[98]

In 1997, Congress passed the FDA Modernization Act.[99] Section 120 of that Act mandates that the Secretary of Health and Human Services establish panels of experts in the fields of science, medicine, and pharmacology, and members of consumer and trade groups to provide expert scientific advice and recommendations

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88. *Id.* at 1171 (stating as an example that "an IND application for a gene therapy mediated by a retrovirus vector would be expected to contain detailed information on the molecular biology of the vector and insert, the production and testing of the producer cell banks, safety testing of the final viral supernatant used for transduction of the patient's cells, and any relevant safety or activity testing in animals. Specifications and required testing at each step of the production process would also be submitted.").

89. *See* Kessler, *supra* note 10, at 1171.

90. *See Senate Hearings*, Dr. Siegel testimony, *supra* note 85, at 58.

91. *Id.* at 45-46.

92. The PI is the lead researcher for the clinical trial.

93. *See Senate Hearings*, Dr. Siegel testimony, *supra* note 85, at 46.

94. *Id.* at 46 (stating that the primary inspection team for clinical trials comes from FDA regional field offices).

95. *FDA to Crack Down on Monitoring Patients Undergoing Gene Therapy*, TRANSPLANT NEWS, Mar. 13, 2000, *available in* LEXIS, News Library.

96. *See* Kessler, *supra* note 10, at 1172.

97. *Id.*

98. *See Senate Hearings*, Dr. Siegel testimony, *supra* note 85, at 46.

99. 21 U.S.C.A. § 355 (n) (West 1999).

to the Secretary regarding the clinical investigation of a drug.[100] The panels' suggestions are not binding on the FDA.[101] Additionally, Senator Edward Kennedy recently proposed legislation to create a new board, the Gene Transfer Safety Symposium, to review all problems that arise from gene therapy trials and to make non-binding recommendations to the FDA.[102] These advisory panels are very similar in composition to the NIH's RAC.

b. The NIH

As with the FDA, the NIH is organized under the Department of Health and Human Services. The NIH was formed as a result of the Public Health Services Act,[103] primarily to promote basic scientific research by providing qualified researchers with federal grant money and by making their results available to other researchers.[104] The NIH is not a regulatory agency per se, but it has come to wield some regulatory authority.[105]

The NIH has oversight over all NIH-funded projects.[106] In addition, if a research institution receives NIH funding, it is subject to NIH regulation of any recombinant DNA (rDNA) research project, whether or not the rDNA project has an NIH grant.[107] Unlike the situation under the FDA, if a private company conducts privately funded rDNA research, the NIH has no authority over the project, although the NIH encourages the company to voluntarily register with the NIH.[108]

Unlike the FDA, which created no new subagency or group to review rDNA projects, the NIH created the RAC in 1974.[109] It was originally designed to review all proposals for NIH-funded research projects involving rDNA.[110] The NIH intended that the RAC be a technical committee to advise the NIH Director on

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100. 21 U.S.C.A. § 355 (n) (1), (3) (West 1999).

101. 21 U.S.C.A. § 355 (n) (8) (West 1999).

102. Aaron Zitner, *Kennedy's Bill Would Create Gene Therapy Oversight Panel: Clinton Administration Also Seeks New Rules for Tests*, BOSTON GLOBE, Mar. 7, 2000, at E5.

103. 42 U.S.C.A. § 201-300 (West 1991 & Supp. 2000).

104. *See* Jaffe, *supra* note 12, at 495-96; *see also* 42 U.S.C.A. §281-99 for code provisions pertaining to the NIH.

105. *See* Wivel & Anderson, *supra* note 67, at 686. Some commentators have called the NIH Guidelines de facto regulations because there is a penalty clause (§ IV.D) for noncompliance. *Id.* Some legal scholars argue that the penalty clause may violate the Administrative Procedures Act, both for its content and because it did not originate from the Department of Health and Human Services. *Id.*

106. *See Gene Therapy: Is There Oversight for Patient Safety: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions*, 106th Cong. 32 (2000) [hereinafter *Senate Hearings*, Dr. Patterson testimony] (statement of Dr. Amy Patterson, Biotechnology Director, National Institutes of Health).

107. U.S. DEP'T OF HEALTH & HUM. SERVS., PUB. HEALTH SERV., NAT'L INST. OF HEALTH, NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES (May 1998) [hereinafter NIH GUIDELINES] § I.C.1.a.

108. *Id.* at § 4.E.

109. *Id.*

110. *Id.* at 496.

scientific issues of working with recombinant DNA.[111] In contrast to the FDA's several "Points to Consider," with which compliance is voluntary, the RAC developed a set of mandatory guidelines for gene therapy that the NIH released in 1976 as the "NIH Guidelines."[112] The NIH Guidelines, which are continually updated, describe an administrative system for performing safe rDNA research.[113] The PI conducting the experiment signs a Memorandum of Understanding and Agreement to perform any trials under the Guideline's safety specifications.[114]

A PI must register human gene therapy protocols with the NIH.[115] The registration requirement's purpose is to ensure that the public has continued access to protocol information and to ongoing data such as adverse clinical effects (adverse events), and long-term follow-up data.[116] As a result, the information that a PI puts in their protocols and adverse event reports potentially becomes available to the public, including competing institutions and private industry.[117]

In 1997, the NIH restructured the RAC so that it now has fifteen members, including scientists and members knowledgeable in law, public policy, ethics, the environment and public health.[118] Members of other federal agencies, such as the FDA and the EPA may sit on the committee as non-voting members.[119] As of October, 1997, the RAC has no approval power over specific human gene therapy protocols;[120] only the FDA can now make such approvals .[121] However, the RAC retains its role as a public forum for issues relating to human gene transfer and recombinant DNA research.[122] Additionally, the NIH continues to promote public

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111. OFFICE OF TECHNOLOGY ASSESSMENT, IMPACTS OF APPLIED GENETICS 316 (1981).

112. *See* Jaffe, *supra* note 12, at 496.

113. *Id.*

114. *Id.*

115. *See* NIH GUIDELINES, *supra* note 107, at app. M. These sections of appendix M requires the PI to describe the treatments that will be administered to the patients and what are the selection criteria for the patients.

116. *Id.*

117. Every gene transfer protocol is available to the public upon request. *See Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 30. Recent amendments to the NIH Guidelines propose the following statement, "[S]erious 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 there are exceptional circumstances." *Id.* at 57.

118. 62 Fed. Reg. 4782-83 (1997). This is a reduction in members from a high of twenty-five, set in 1986. 51 Fed. Reg. 16, 958-85 (1986).

119. 62 Fed. Reg. 4783 (1997).

120. 62 Fed. Reg. 59,032 (1997). There is an exception for protocols that at least three members of the RCA decide are sufficiently novel or controversial enough to justify public disclosure. 62 Fed Reg. at 4783.

121. The FDA has statutory authority to approve or disapprove protocols under the FFDCA at 21 U.S.C.A. § 355 (West 1999).

122. *See* Judith E. Beach, *The New RAC: Restructuring of the National Institutes of Health Recombinant DNA Advisory Committee*, 54 FOOD & DRUG L.J. 43, 43 (1999). The NIH also added a new discussion and comment forum, called the Gene Transfer Policy Conferences (GTPCs), which assemble participants with scientific, ethical and legal experience to discuss a single issue in human gene therapy. 62 Fed. Reg. at 59,033. There are no permanent members on the GTPCs and their findings and recommendations are made public. *Id.*

accountability for human gene therapy experiments by publishing a database of human gene transfer clinical trials.[123]

c. Interface Between the NIH and the FDA

Research institutions that receive NIH grants must follow the NIH guidelines for any human gene therapy trials, including submitting a protocol to the RAC. They must also file an IND application with the FDA.[124] Private firms that receive no NIH grant money need not file a protocol with the NIH, although they may voluntarily file, and the NIH encourages them to do so.[125] Once the FDA grants the PI permission to proceed, he or she must submit a written report to the NIH that includes how the PI responded to any RAC recommendations on the research protocol, and any changes that the FDA required in the protocol.[126] In the event that there are any adverse events, i.e. deaths or serious side effects, the PI must notify both the FDA and the NIH.[127]

2. Tort Law Issues

A comprehensive examination of how to best regulate gene therapy must also include a look at tort law issues. Whether or not the physician-researcher or a product manufacturer complies with federal regulations for performing human gene therapy, they are potentially liable under tort law for a patient's injuries caused by gene therapy.[128] The two major tort law theories that will have the greatest impact on human gene therapy are the theories of informed consent and strict product liability.

Under the informed consent doctrine, a patient can sue a physician for failure to obtain the patient's informed consent for a medical procedure.[129] The premise for an informed consent cause of action is that the physician did not provide the patient with enough information about the risks of the proposed treatment or procedure to enable the patient to make an informed and intelligent decision about his or her medical care.[130] Courts have extended the informed consent doctrine to require physicians, before treatment, to disclose to patients any personal economic or research interests that the physician has that may affect his medical judgment.[131] In

123. *See* Beach, *supra* note 122, at 49-50.

124. *See* Kessler, *supra* note 10, at 1171-71.

125. *See* NIH GUIDELINES, *supra* note 107, at § IV.E.

126. *Id.* at app. M.

127. *See Senate Hearings,* Dr. Patterson's testimony, *supra* note 106, at 29.

128. DAN D. DOBBS, LAW OF TORTS § 373 (2000).

129. *See* DIAMOND, *supra* note 15, at 103.

130. *Id.* at 104.

131. The seminal case in California regarding disclosure of physician conflict of interest, whether economic or research in nature, is *Moore v. Regents of the University of California*, 793 P.2d 479 (Cal. 1990) (holding, "[A] physician who is seeking a patient's consent for a medical procedure must, in order to satisfy his fiduciary duty and

addition to the physician; the physician's employer would potentially be liable to the injured patient under the tort theory of respondeat superior.[132]

Both the FDA and the NIH's RAC regulate the informed consent process for human gene therapy clinical trials.[133] The FDA reviews the information to be disclosed to the patient in the consent form, and frequently instructs the PI to include additional information.[134] Additionally, the FDA verifies that the PI has submitted the forms to the FDA, and that the forms have been signed by the patient.[135] The RAC evaluates the entire process, including the protocol, the forms, how the patient is told about the risks and by whom, and then forwards its recommendations to the individual Institutional Review Board (IRB)[136] responsible for the clinical trial.[137] Again, despite the often careful federal agency scrutiny of the information contained in the patient consent documents, compliance with federal regulations will not be sufficient to shield physicians from liability if they fail to disclose information that a reasonable patient would think is material to their decision to undergo treatment.[138]

Another possible theory of tort liability for companies manufacturing gene therapy products is strict product liability. Under the strict product liability theory, the manufacturer of a defective product is strictly liable in tort for the injuries that product causes to the user.[139] Justice Traynor of the California Supreme Court presented the reasoning behind this theory in *Escola v. Coca Cola Bottling Co.*[140] First, the manufacturer is in a better position than is the consumer to foresee and reduce product-related injuries.[141] Second, the manufacturer can insure against the risk of injury and pass the cost to the consumer in the form of higher prices.[142] Finally, given the complexities of modern manufacturing, it is too difficult for a

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to obtain the patient's informed consent, disclose personal interests unrelated to the patient's health, *whether research or economic*, that may affect his medical judgement.") (emphasis added).

132. *See* DIAMOND, *supra* note 15, at 221.

133. *Gene Therapy: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions*, 106th Cong. 55-56 (2000) (statements of Dr. J.P. Siegel, Director, Office of Therapeutics, FDA and Dr. Amy Patterson, Biotechnology Director, National Institutes of Health).

134. *See Senate Hearings*, Dr. Siegel testimony, *supra* note 85, at 56.

135. *Id.*

136. The Institutional Review Board, charged with protecting patients from unnecessary risk, is one of two local committees charged with local oversight for a NIH-directed human gene therapy protocol. The other committee is the Institutional Biosafety Committee (IBC), charged with oversight of the scientific aspects of the protocol and laboratory and environmental safety. *See* Wivel & Anderson, *supra* note 67, at 676.

137. *See Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 56.

138. *See* DOBBS, *supra* note 128.

139. *See* RESTATEMENT, *supra* note 16 §402A. Under the Restatement, a plaintiff must show that there was a sale of a product, that the plaintiff was injured by the product, and that there was a design, manufacturing or warning defect with the product that caused the plaintiff's injury. *See* DIAMOND, *supra* note 15, at 329-37 (explaining that different jurisdictions use different tests to judge whether a design defect exists in the product).

140. 150 P.2d 436, 440-44 (Cal. 1944) (Traynor, J., concurring).

141. *Id.* at 440-41.

142. *Id.* at 441.

consumer to identify and prove negligent conduct.[143] Strict liability in tort is now the generally accepted standard for product liability in the United States.[144]

The Restatement (Second) of Torts section 402A, comment k, recognizes an exception for "unavoidably unsafe" products. The Restatement drafters recognized that some classes of products are beneficial to society even if they cannot be made completely safe for ordinary and intended use.[145] One such class of unavoidably unsafe products is pharmaceutical drugs.[146] Many states have adopted portions of the Restatement's comment k to exempt pharmaceutical drugs from strict product liability for design defects.[147] However, even in these jurisdictions, prescription drug makers are still liable for manufacturing defects or for failing to warn of known or reasonably knowable side effects.[148] Other jurisdictions adopt a case-by-case analysis to determine whether to exempt a drug from strict product liability.[149]

Gene therapy may be similar to pharmaceutical drugs with regard to balancing cost versus benefit to decide whether gene therapies should be exempt from liability for design defects. However, in the absence of any superceding federal statutory protection, each state must decide for itself whether or not to extend this protection to gene therapy products. Such a process usually involves costly, state-by-state court battles.

Some commentators argue that Congress should act to prohibit strict liability in tort for gene therapy.[150] They suggest that the biotechnology industry should be considered a strategic industry and thus deserving of special consideration.[151] Strategic industries are those that are fundamental to an entire industrial sector, perhaps even fundamental to the economic success of the nation.[152] The U.S. Department of Commerce identified biotechnology as an emerging technology that is expected to be of great economic importance.[153] However, the threat of excessive tort liability remains an obstacle to industry growth.

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143. *Id.*

144. *See* RESTATEMENT, *supra* note 16, at § 402A.

145. *Id.* at cmt. k.

146. *Id.*

147. *See* Brown v. Superior Court (Abbott Laboratories), 751 P.2d 470, 476 (Cal. 1988) (explaining that its reasons to foreclose strict product liability for prescription drugs included encouraging the development of new prescription drugs, maintaining an affordable price for prescription drugs, and not unduly delaying to delivery of such drugs to the public).

148. *Id.* at 483 n.12.

149. *See* Saving v. Sterling Drug, Inc., 795 P.2d 915 (Kan. 1990); White v. Wyeth Laboratories, Inc., 533 N.E. 2d 748 (Ohio 1988).

150. *See generally* Dan L. Burk & Barbara A. Boczar, *Biotechnology and Tort Liability: A Strategic Industry at Risk*, 55 U. PITT. L. REV. 791 (1994) (suggesting that biotechnology be exempt even from negligence standards of liability). This Article limits consideration of liability exemption to strict product liability for design defects only.

151. *Id.* at 829.

152. Glenn H. Reynolds & Robert P. Merges, *Toward an Industrial Policy for Outer Space: Problems and Prospects of the Commercial Launch Industry*, 29 JURIMETRICS J. 7, 9-10 (1988).

153. U.S. DEP'T OF COMMERCE TECHNOLOGY ADMINISTRATION, EMERGING TECHNOLOGIES: A SURVEY OF TECHNICAL AND ECONOMIC OPPORTUNITIES 3 (1990).

B. Troubles With the Current System

Under the current system of regulating gene therapy there are multiple problems for all of the participants: the public; the regulating agencies; and the gene therapy companies and researchers. There are concerns about patient safety, confidentiality of patient information, agency effectiveness, a lack of clear, adequate oversight for the industry, and a need for protection of proprietary information.

The two most important problems facing the public in gene therapy clinical trials are lack of informed consent, and a concern about the public availability of confidential patient information. With regard to informed consent, the United States General Accounting Office stated that "an inherent conflict of interest exists when physician-researchers include their [own] patients in research protocols."[154] Senator Dodd suggested recently that one factor contributing to this inherent conflict of interest is a patient's reluctance to ask their doctor important questions for fear that the doctor or researcher will be irritated or offended and may drop the patient from the trial.[155] Senator Frist, a physician, stated that although the risks and benefits of the treatment are written on the consent form, the physician can emphasize some things and de-emphasize others; "there can be real bias in that room."[156]

Recently, this issue arose during a hearing by the Senate Subcommittee on Public Health.[157] During the hearing, Paul Gelsinger, father of a boy who died as a result of gene therapy in September 1999, claimed several misrepresentations by researcher-physicians in that trial. Mr. Gelsinger stated that no one had told him that there had been no successes in those trials; he thought that the therapy worked.[158] He said that researchers told him that one patient in a previous trial had improved fifty percent as a result of the treatment; this information was false.[159] Mr. Gelsinger stated that researchers told him that the most dangerous parts of the procedure were

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154. GENERAL ACCOUNTING OFFICE, SCIENTIFIC RESEARCH: CONTINUED VIGILANCE CRITICAL TO PROTECTING HUMAN SUBJECTS, (Washington D.C.; General Accounting Office, GAO/HEHS-96-72, Mar. 8, 1996). *See also* Larry R. Churchill et al., *Genetic Research as Therapy: Implications of "Gene Therapy" for Informed Consent*, 26 J.L. MED. & ETHICS 38, 44-45 (1998) (tracing the history of informed consent and arguing that the "false promise" of success and the hype about clinical trials of gene therapy fail to sufficiently inform the patient about the current true potential benefits from gene therapy).

155. *Gene Therapy: Is There Oversight for Patient Safety: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions*, 106th Cong. 22-23 (2000) [hereinafter *Senate Hearing*, Senator Dodd statement] (statement of Senator Christopher Dodd, D-Ct).

156. *Gene Therapy: Is There Oversight for Patient Safety: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions*, 106th Cong. 55 (2000) (statement of Senator Frist, R-TN).

157. *Gene Therapy: Is There Oversight for Patient Safety: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions*, 106th Cong. 76 (2000) [hereinafter *Senate Hearings*, Dr. Walters testimony] (statement of Dr. LeRoy Walters, Director of the Kennedy Institute of Ethics, Georgetown University) (expressing concern that gene therapy patients often are not told about how new the science of gene therapy is, and how remote are the chances that the current patients will reap any benefit from the treatment).

158. *See Senate Hearings*, Gelsinger testimony, *supra* note 1, at 8.

159. *Id.*

the liver catheterization and the follow-up liver biopsy.[160] He said that there was no reference in the consent materials to animals dying of liver injury in the trials, information that had previously appeared in the documents.[161] Mr. Gelsinger felt that the researchers were willing to take greater risks with patients' health because they were close to a cure.[162] If true, this is a conflict of interest between the researchers' need for clinical trial volunteers and the potential patient's need for information. It is possible that Mr. Gelsinger simply misunderstood what he was told, or was afraid to ask difficult questions. Perhaps the omissions and misrepresentations were only due to administrative carelessness. Perhaps they were due to a deliberate attempt by researchers to attract more volunteers, at any cost, to further their research when they were very close to success. In any case, the informed consent process failed Mr. Gelsinger and his son.[163]

The confidentiality of patient information is a concern for researchers and the public alike. Researchers performing clinical trials are concerned that the confidential patient information that both the FDA and the NIH require the researchers to submit with their protocols may be made public via the NIH.[164] Although federal law prohibits the FDA from revealing confidential patient information,[165] the NIH has no such restriction. The purpose of the NIH is to gather and disseminate information on advances in government-funded scientific research,[166] including all information from the protocols or adverse event reports, whether or not it is confidential.[167] Therefore, there is potential public access to confidential patient information via the NIH.

There are also concerns with the agencies that currently regulate gene therapy trials, including inadequate researcher compliance in reporting adverse events in the clinical trials, unsuccessful oversight of the informed consent process, lack of resources or jurisdiction to effectively police rapidly changing clinical trials, and interagency rivalry.

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160. *Id.*

161. *Id.*

162. *Id.* at 22.

163. *But see Senate Hearings*, Kast testimony, *supra* note 64, at 11 (stating that he felt that the informed consent report that he signed prior to his treatment was a "clear and strong statement" of the risks.). Mr. Kast read one such informed consent form, provided by Johns Hopkins University, which said:

> We do no know what the risks are when people are given the altered AAV virus with the CFTR gene. The altered virus could spread to other parts of your body. The consequences of this are not known at this time. There is a very small chance that the altered virus could damage the DNA in the cells of your lungs or nose. If this happened, it could put you at risk for developing cancer in the future. You will receive no therapeutic benefit from this. Side effects in humans are not known. If you should die either during or after the study, we will ask your family for permission for an autopsy.

Id.

164. *See* NIH GUIDELINES, *supra* note 107, at § IV.E.2-5 (b).

165. *See* Henderson, *supra* note 49.

166. *See Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 29.

167. *See* NIH GUIDELINES, *supra* note 107, at § IV.E.2-5 (b).

Despite the fact that researchers must report any serious adverse effects to both the FDA and the NIH,[168] they are often failing to report to the NIH.[169] Recently, an NIH official described the situation with regard to reporting serious adverse effects to the NIH as "widespread noncompliance."[170] When the NIH sent out a letter in late 1999 asking for reports on all serious adverse events that occurred solely during protocols involving adenovirus vectors,[171] it received reports of 652 previously unreported adverse events.[172] FDA and NIH officials believe that most of the adverse events were due to the progression of the underlying illness, surgery, or other treatments, not to the gene therapy treatments.[173] Despite this fact, the figures show that researchers' reporting of adverse events, at least to the NIH,[174] is grossly inadequate, especially in light of the fact that adverse events form one component of the risk supposedly disclosed in the patient's consent form.[175]

The second major agency-related concern is unsuccessful oversight of the informed consent process. As to FDA oversight of informed consent, one FDA representative admitted that he could not say that the FDA was satisfied with the results of the its policies and practices regarding informed consent.[176] The PI must submit to the FDA and to the IRB a proposed informed consent form for a gene therapy clinical trial.[177] Both the IRB and the FDA rely to some extent upon one another to ensure that all of the appropriate information is in the consent form.[178] However, the PI and the IRB may lack access to the results, including adverse events, of clinical trials done at other institutions, and thus may not know about important risks that they ought to include in their consent forms.[179] Because all PIs must report adverse events to the FDA, the FDA has access to important risk information that PIs and IRBs lack. Given the FDA's awareness of all clinical trials'

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168. *See Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 29.

169. One reason that researchers are reluctant to report adverse events to the NIH is the fear of public access to their proprietary information. *See* Henderson, *supra* note 49.

170. *See Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 29.

171. Adenovirus vectors account for approximately 25-30% of the current clinical trials. *See Senate Hearings* Dr. Verma testimony, *supra* note 5 at 63.

172. *Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 47-8. These adverse events occurred over a seven-year period. *Id.* at 48. Of 464 adverse events, only 85 were considered to be serious. *See* Henderson, *supra* note 49.

173. *Gene Therapy: Is There Oversight for Patient Safety: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions,* 106th Cong. 49 (2000) (statements of Dr. J.P. Siegel, Director, Office of Therapeutics, FDA, and of Dr. Amy Patterson, Biotechnology Director, National Institutes of Health).

174. *See Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 29 (explaining that adverse events must be reported to NIH immediately).

175. *See* NIH GUIDELINES, *supra* note 107, at app. M.III.B.1(e).

176. *See Senate Hearings*, Dr. Siegel testimony, *supra* note 85, at 56.

177. *Id.* at 56.

178. *Id.*

179. Although the NIH has a database, accessible via the Internet, that tracks adverse events occurring in clinical trials for all NIH-funded research, many times researchers fail to report adverse events to the NIH. *See Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 35.

adverse events nationwide, the FDA may be neglecting to verify that the consent form adequately characterizes the patient's risk.[180]

The NIH's RAC also reviews the consent forms.[181] Unfortunately, given the researchers' noncompliance with NIH reporting requirements, the RAC cannot accurately verify whether or not the risks stated in the consent forms are correct. Therefore, neither the NIH nor the FDA currently protects clinical trial patients as well as they ought.

The third major agency-related concern with gene therapy regulation is a lack of resources to effectively police rapidly changing clinical trials. The NIH is not a regulatory agency, and thus is not equipped to actively police the protocols that they fund. The NIH has no enforcement arm, no field inspectors, and no way to punish violations except for the penalty of discontinuing its funding grant to the research institution in the event of noncompliance with the NIH Guidelines.[182] In the case of large biotechnology or pharmaceutical companies that do not apply for NIH grants, the NIH has no authority over the clinical trials at all, though it encourages the private companies to voluntarily comply with NIH Guidelines.[183]

Despite the problems with the NIH overseeing human gene therapy clinical trials, the NIH's RAC is highly respected worldwide for its integrity and scientific expertise, especially concerning gene therapy protocols.[184] The RAC has not only scientific expertise, but also ethical and legal experts as members.[185] Thus, it has scientific, legal and ethical expertise and the respect of the international scientific community, but it lacks both the resources and the jurisdictional grant to effectively regulate gene therapy trials and commercial use.

Unlike the NIH, the FDA has an efficient enforcement mechanism to ensure compliance with its regulations; the industry and public research institutions alike fear the consequences of the FDA discovering a violation of its regulations.[186] However, the FDA lacks sufficient staff members with expertise in this highly sophisticated science to effectively police compliance with FDA regulations.[187] FDA administrators say that the science changes so rapidly, it is difficult for them the stay

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180. This situation may result from insufficient FDA resources, coupled with the statutory prohibition against the FDA disclosing confidential or proprietary information. *See Senate Hearings*, Dr. Siegel testimony, *supra* note 85, at 46, 58; *see also* Henderson, *supra* note 49.

181. *See Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 56.

182. *See* Wivel & Anderson, *supra* note 67, at 686.

183. *See* NIH GUIDELINES, *supra* note 107, at § IV.E.

184. *See Senate Hearings*, Dr. Walters testimony, *supra* note 157, at 83; *House Hearings*, Dr. Abbott testimony, *supra* note 43, at 158 (saying, "It is obvious that many participants in gene therapy development have their own interests at heart (e.g., academic institutions, scientists, vector manufacturers, etc.), but the RAC is the independent body that has no vested interest and no ax to grind. It is there solely to protect the public.").

185. 62 Fed. Reg. 4782-83 (1997).

186. *Gene Therapy: Is There Oversight for Patient Safety: Hearings Before the Subcomm. On Public Health of the Senate Comm. On Health, Education, Labor and Pensions*, 106th Cong. 96 (2000) (statement of Mr. Stewart Parker, President and CEO, Targeted Genetics Corp.).

187. *Senate Hearings*, Dr. Siegel testimony, *supra* note 85, at 46.

abreast of the changes.[188] There are insufficient resources to physically inspect all of the gene therapy clinical trials.[189] In addition, there are concerns that the FDA cannot adequately address the ethical ramifications of human gene therapy.[190] Lastly, there have been accusations that business interests have unduly influenced the FDA, causing the FDA to be less impartial than it should be.[191]

Although both the NIH and the FDA have advantages over the other in regulating gene therapy, both agencies currently have considerable disadvantages. Dr. LeRoy Walters, Director of the Kennedy Institute of Ethics at Georgetown University, suggests that it may be unrealistic to expect one regulatory agency alone to perform this role.[192]

There is also a concern over interagency rivalry. An overlap in jurisdiction exists between the FDA and the NIH, and there may be a power struggle over which agency will regulate human gene therapy.[193] The FDA has stated that the DNA used in human gene therapy trials will be considered a biological drug subject to FDA regulations even if reviewed by the RAC.[194] One commentator recently said, "on several critical matters, there's been a lack of appropriate cooperation between the FDA and the NIH."[195] It is problematic to rely on interagency cooperation to remedy defects in the regulatory process. What agency administrator would suggest giving up some bit of control to another agency? To do so would be professionally perilous. To rely on the cooperation of two federal agencies to cure the problems of human gene therapy regulation would be misguided.

Lastly, the human gene therapy industry is caught in a paradoxical plight: in order to justify the cost of human gene therapy research, firms must be able to protect and capitalize upon their proprietary human gene therapy information; however, researchers often must include proprietary information to the FDA and the NIH[196] in their adverse event reports, and the NIH must make adverse event information available to other researchers, thus potentially making proprietary information public.[197]

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188. *Id.*

189. *Id.*

190. *See* Beach, *supra* note 122, at 50.

191. *See Senate Hearings*, Gelsinger testimony, *supra* note 1, at 17.

192. *See Senate Hearings*, Dr. Walters testimony, *supra* note 157, at 76.

193. *See* Jaffe, *supra* note 12, at 518 (stating that there were signs of a power struggle between the FDA and the NIH).

194. 49 Fed. Reg. 50,880 (1984).

195. *See Senate Hearings*, Dr. Walters testimony, *supra* note 157, at 76.

196. *See* NIH GUIDELINES, *supra* note 115, at app. M.VIII.B. (Requiring reports following "any serious adverse event...").

197. *See Senate Hearings*, Dr. Patterson testimony, *supra* note 106, at 57 (stating, "The position of the RAC to date has been that adverse event reports belong in the public domain so that they can inform other investigators, they can inform prospective patients. The RAC has held to that principle.").

In order to bring a new drug to market, it costs a company from $300 million to $600 million to develop and take the drug through the FDA regulatory process.[198] Accordingly, drug companies need to establish strong intellectual property rights before they proceed to market or they will not be able to recover their research and development costs.[199] Although the exact cost of bringing to market human gene therapy products is yet unknown,[200] the business reality remains the same: safeguard your ability to recover your research costs by protecting your intellectual property rights. A company cannot protect its intellectual property rights if its proprietary information is made public prior to patenting.[201] While statutes prohibit the FDA from making proprietary information public, the NIH must do so.[202] Therefore, if a researcher must submit his or her protocols to the NIH for approval, there is a risk of public access to proprietary information, resulting in lost intellectual property rights. The upshot is that researchers are reluctant to report to the NIH.[203]

Furthermore, a researcher must submit protocols to both the FDA and the NIH, yet each must be in a different format. Even the requirements for reporting adverse events differ between the NIH and the FDA.[204] Jeff Isner, M.D., gene therapy researcher at St. Elizabeth's Medical Center in Boston, Massachusetts, said, "[there] has been a tremendous amount of ambiguity about what needs to be reported to the NIH."[205] Conversely, Dr. Isner said, "I think that every individual, institution and company doing gene therapy understands very clearly" what the FDA regulations entail.[206]

In sum, there are problems for all of the participants of human gene therapy regulation. The clinical trial patients, the federal agencies involved in regulation, and the gene therapy industry are all feeling the effects of these regulatory concerns.

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198. Jim Conley, *Patenting the Blueprint of Life,* PCCOMPUTING FROM ZDWIRE, May 1, 2000, *available in* 2000 WL 2000299.

199. *Id.*

200. To date, no human gene therapy products have come to market. *See* Papanikolaw, *supra* note 55 and accompanying text.

201. The Patent Act states, "A person shall be entitled to a patent unless—(b) the invention was . . .in public use . . .in this country . . .more than one year prior to the date of application for patent in the United States. . . ." 35 U.S.C. § 102 (West 1999). In addition, trade secret information loses its proprietary value if it becomes publicly known. *See* Uniform Trade Secrets Act § 1 (4) (ii); *see also* Metallurgical Industries, Inc. v. Fourtek, Inc., 790 F.2d 1195, at 1200 (5th Cir. 1986) (discussing the problems with the current system of regulating gene therapy).

202. *See supra* Part III.B.

203. *See* Henderson, *supra* note 49.

204. *See Senate Hearings*, Dr. Siegel testimony, *supra* note 85, at 40.

205. *NIH Gene Therapy AE Reporting Standards Less Clear Than FDA*, BLUE SHEET, Mar. 22, 2000, *available in* 2000 WL 8519047.

206. *Id.*

IV. ALLEVIATING THE PROBLEMS

Given that biotechnology is a strategic industry and thus deserving of special consideration,[207] and given the concerns with the current regulatory system, we must examine the problem of regulation anew. Therefore, instead of attempting to fit regulation of gene therapy into the existing framework, it may be better to look at the puzzle afresh and ask what regulatory framework would be best now, yet will be flexible enough to change as the industry grows.[208] Any proposals to regulate human gene therapy trials and treatment should address the subject as a whole, accounting for the interests of the public, the industry and the regulating agencies.

There are several obvious requirements for a regulatory structure: scientific expertise that paces the industry; authority to make and enforce regulations; flexibility to accommodate extremely rapid technological innovations; input on regulations from persons with backgrounds in ethics, law, public policy and public health to provide a balanced viewpoint; and the ability to share scientific innovation while protecting proprietary information. Accordingly, this Article briefly describes five possible regulatory changes to deal with the problems of the industry. First, the Senate Committee for Health, Education, Labor, and Pensions should establish a standing Senate Subcommittee for biotechnology issues. Second, the RAC should be moved directly under the Secretary of Health and Human Services, with the authority to direct the FDA and the NIH regarding biotechnology issues. Third, the Department of Health and Human Services should increase FDA resources for monitoring and enforcing biotechnology regulation. Fourth, the FDA should establish regulations to mandate the appointment of independent patient advocates for patients considering participating in gene therapy clinical trials. Lastly, Congress should prohibit strict product liability for design defects in gene therapy products.

A standing Senate sub-committee for biotechnology issues within the Senate Committee on Health, Education, Labor, and Pensions would help with some of the major problems of this young industry. Although the human gene therapy industry shares many of the characteristics, and even some of the same firms, as the pharmaceutical industry, it is fundamentally more complex, with concomitantly greater unknown consequences. There are ethical considerations that must be openly debated: who will have access to this type of therapy given limited resources for medical treatment and the focus on cost containment; should insurance pay for these treatments; should Congress prohibit gene therapy for human enhancement?[209] Therefore, this fledgling industry needs greater Congressional oversight at this time

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207. *See supra* notes 150-53 and accompanying text.

208. It is unlikely that industry or institutional researchers will be willing to challenge the current system. Who would risk NIH funding or FDA approval to criticize?

209. *See House Hearings*, Dr. Abbott testimony, *supra* note 43, at 122 (questioning how we as a nation should ration "technically feasible but commercially impractical treatments," who should pay for them, and what should be done about germline transfer).

than would be the case if it were a more mature industry. This proposed subcommittee should periodically assess public health issues and industry issues regarding human gene therapy, such as public safety and additional funding for research. It could write appropriate legislation, including new jurisdictional and enabling statutes, as needed.[210]

Second, as suggested by Dr. LeRoy Walters of Georgetown University, the RAC should be moved from the NIH and made to report directly to the Secretary of Health and Human Services.[211] The RAC's regulatory directives should be binding on both the FDA and the NIH via the Secretary of Health and Human Service's office. Also, the new RAC must be able to monitor FDA and NIH compliance with RAC directives. RAC membership should rotate to ensure member-scientists are active researchers. Because the RAC's directives would be binding on the FDA and the NIH, each of those agencies' representatives should have voting rights in the new RAC and could provide administrative and regulatory expertise.

The new RAC should standardize both the protocol reporting forms and the adverse event reporting forms of the FDA and the NIH. This would allow researchers to complete one form for protocols and one for adverse event reporting that they could send to both agencies. Information that is common to both agency standards could be listed first, with agency-specific information listed thereafter. The forms should segregate confidential and proprietary information to make it easily separable. Researchers could electronically file their protocol and adverse event reports directly with the new RAC.[212] The new RAC could limit access to the filings, or portions thereof, as necessary.

This second proposal would aid in the trouble of interagency rivalry by using the power of the Secretary of Health and Human Services to ensure that the new RAC's regulatory directives have binding effect on both the FDA and the NIH. Neither the FDA nor the NIH would direct the other, nor would problem solving depend on voluntary interagency cooperation. Further, the suggestion would preserve the current RAC's flexibility, impartiality, its scientific, ethical and legal expertise, and its respect by the international scientific community.[213] It also would allow the FDA to continue as the well-respected regulatory enforcement mechanism for gene therapy. This recommendation would also aid the industry by streamlining

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210. *See* Brian C. Cunningham, *Impact of the Human Genome Project at the Interface Between Patent and FDA Laws*, 7 RISK: HEALTH SAFETY & ENV'T 253, (1996) (writing that, although it may be worse for Congress to pass legislation which might impede research, the absence of legislation in this area forces agencies "to retrofit existing, inadequate legislation to deal with policy issues surrounding recombinant DNA and has slowed innovation due to industrial concerns over the lack of a clear regulatory path.").

211. *See Senate Hearings*, Dr. Walters testimony, *supra* note 157, at 83-84. Dr. Walters is a former Chairperson of the RAC's Human Gene Subcommittee.

212. In the alternative, researchers could send their adverse event report forms directly to a staff member of the new RAC, which would maintain the database of adverse events. RAC staffers could scan adverse event reports into a secure computer file that only selected FDA and NIH personnel could access, thus making the reports immediately available to both agencies.

213. *See supra* note 184 and accompanying text.

its reporting requirements. At the same time, it would make reporting easier for the federal agencies, yet facilitate keeping confidential and proprietary information just that, confidential and proprietary.

This proposal is similar to the one made by Senator Edward Kennedy recently when he proposed the Gene Transfer Safety Symposium (GTSS).[214] However, unlike the GTSS, the relocated RAC could cause its regulatory directives to be binding on the FDA and the NIH. The proposed GTSS would duplicate the scientific, legal and ethical expertise of the RAC without providing it with any authority to achieve anything but non-binding suggestions. The GTSS would preserve the status quo; the new RAC would change it.

Third, the Department of Health and Human Services should increase the FDA's budget to provide for more resources for monitoring and enforcing biotechnology regulation. Dr. J.P. Siegel, Director of the FDA's Office of Therapeutics, recently explained that part of the difficulty with the FDA's oversight of gene therapy was due to a shortage of personnel knowledgeable in rapidly changing biotechnology.[215] He also proposed that the FDA increase its inspectional oversight of gene therapy INDs. The FDA currently employs 150 to 200 clinical trial inspectors, but it has never asked them to assess patient safety monitoring in gene therapy trials.[216]

With this third proposal for increased funding, the FDA could hire more scientists knowledgeable in gene therapy, increase its investigations of clinical trials, and do more patient safety regulation, thus better protecting clinical trial patients. At the same time it would allow the industry to continue under a familiar regulatory agency.

Fourth, the FDA should establish a regulation to mandate the appointment of independent patient advocates for patients considering participation in gene therapy clinical trials. If it is often difficult for a patient to understand the risks and benefits of participating in a new drug clinical trial; how much more difficult it must be for a patient to understand and appreciate the risks and benefits of participating in a gene therapy clinical trial. Paul Gelsinger, father of the teenager who died last year as a result of gene therapy, recommended that a patient advocate be present when a clinical researcher discusses the information on the consent form with the prospective gene therapy patient.[217] Senator Dodd described this patient advocate as "someone there [in the patient-doctor meeting] with that cold eye who will go down that list of tough questions and ask them."[218] In order to know what tough questions to ask, a patient advocate should be familiar with gene therapy, the protocols for treatment, and all reported adverse events.

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214. *See* Zitner, *supra* note 102 and accompanying text.

215. *See Senate Hearings*, Dr. Siegel testimony, *supra* note 85, at 46.

216. *FDA to Crack Down on Monitoring Patients Undergoing Gene Therapy*, TRANSPLANT NEWS, Mar. 13, 2000, *available in* LEXIS, News Library.

217. *See Senate Hearings*, Gelsinger testimony, *supra* note 1, at 18.

218. *Senate Hearing*, Senator Dodd statement, *supra* note 155 at 23.

This fourth proposal would increase the prospective patient's understanding of the informed consent process. It benefits researchers in that it would reduce the likelihood of having to defend an informed consent medical malpractice suit, and would allay the taint of a physician-researcher advising a patient while having a monetary or research interest in the outcome of the patient's decision.

Finally, Congress should provide protection from oppressive tort liability by prohibiting strict product liability for design defects of human gene therapy treatments. This proposal is not a call to prohibit liability for negligence in the manufacture or administration of gene therapy treatments. This recommendation would merely limit strict product liability to manufacturing defects and failure to warn of known or reasonably knowable side effects.[219] This would clearly benefit companies that make gene therapy products. Some commentators argue that prohibiting strict product liability is essential to protecting a strategic industry from an unreasonable burden of tort liability.[220] Fostering the development of the biotechnology industry, including human gene therapy, would potentially yield significant benefits not only to biotechnology, but also to other economic sectors that are tied to biotechnology.[221] Yet, it would also benefit the seriously ill patients by making available a therapy that would not otherwise exist or only be available at a prohibitively high cost.[222] In addition, gene therapy is consistent with modern medical goals of providing preventative and corrective medicine.[223] Congress is the best place to make a decision such as this one that requires balancing conflicting policy interests.

V. CONCLUSION

Human gene therapy has presented many new opportunities for health care advancement. Along with the potential benefits, the problems of a newly emerging scientific field inevitably exist. The regulatory agencies' legal approach taken to deal with the new research has also created problems for the industry. Although there has been much discussion recently about the current inadequacies of regulation in gene therapy, given the limitation in resources and enabling legislation, both the NIH and the FDA have done well regulating such a new, untested science. However, now is the time to take a fresh look at regulating gene therapy before there are more deaths. We must balance the interests of all of the interested parties, the patients and the public, the industry and its researchers, and the regulatory agencies. Now is the time to change to a regulatory framework that is light, fast, and flexible.

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219. *See* Brown v. Superior Court (Abbott Laboratories), 751 P.2d at 483 n.12 (Cal. 1988).
220. *See* Burk & Boczar, *supra* note 150, at 805.
221. *Id.* at 800.
222. *See Brown*, 751 P.2d at 479.
223. *See House Hearings*, Dr. Greenwood testimony, *supra* note 61, at 14.

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