A False Start? The Impact of Federal Policy on the Genotechnology Industry

Michael J. Malinowski and Maureen A. O'Rourke†

Important scientific discoveries in the field of human genetics have been reported in the nation's major newspapers since the beginning of the decade, and these discoveries have given rise to a multi-billion dollar industry. Mr. Malinowski and Professor O'Rourke explore the impact of federal policy on the field and the resulting industry. They argue that federal policy in support of genetics research and development has not been followed by the introduction of regulatory and health policy necessary for the efficient and responsible commercialization of the industry's products. As a consequence, Mr. Malinowski and Professor O'Rourke suggest, federal policy may have given rise to a "false start" for the industry. The authors suggest that, in light of the potential impact of genetics products on human health and the societal and ethical implications of said technologies, ignoring the policy and regulatory questions surrounding genetics products is, at best, irresponsible. Mr. Malinowski and Professor O'Rourke identify many of the regulatory shortcomings and offer a series of reforms and suggestions to foster the responsible commercialization of the forthcoming generation of genetics products.

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†Maureen O'Rourke is an Associate Professor of Law at the Boston University School of Law ("BUSL"), and Michael Malinowski is an associate at the Boston office of Kirkpatrick and Lockhart. The opinions expressed herein are the authors' unless attributed to others. Special thanks to Patricia A. Jones, Senior Vice President, Feinstein Partners, Inc., for sharing her insights in the fields of biotechnology, economics, and the health care industry, and for providing valuable research materials. Thanks also to Michael J. Astrue, Katheryn L. Biberstein, Ron Cass, Carmela Correale, Dr. James Dickson, Estelle Favor, Jennifer Fluet, Dan Freehling, Mark A. Hofer, Eric Karich, Hon. Michael Kirby, Patricia Kuszler, David Lyons, Mary Mahowald, Noreen Martin, Fran Miller, Richard Mural, Bob Seidman, David Seipp, Donna Shea, Evelyn Shen, Lucia Silecchia and all the participants in the BUSL Faculty Workshop series for their comments, support, and advice. Our appreciation to Thomas F. Holt, Jr., Louis C. Miller, and Joan Devereaux for supporting this project. Finally, thanks to the BUSL library and Copy Center staffs and to Evan Berg, Michael Bowse and Stacy Jacob for their research assistance.

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Introduction

Genotechnology is the subset of biotechnology concerned with human genetics and associated with the scientific efforts and advances of the Human

Genome Project (HGP).[1] The business of genotechnology is big money, applied medicine, and as American in origin as the automobile industry and Microsoft.[2] Biotech-related products generated annual sales of more than $7 billion in 1993, approximately $7.7 billion in 1994, and $8.7 billion in 1995.[3] The total market for deoxyribonucleic acid (DNA) diagnostics is expected to exceed $700 million by 1998[4] and could be much greater in the near future.[5] A single successful drug, like Amgen Inc.'s[6] anemia-fighting protein, Epogen,

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1. HGP is discussed *infra* Section II.A. The use of the term "genotechnology" is necessitated by the extreme breadth of the term "biotechnology," which has been defined as "any process in which organisms, tissues, cells, organelles, or isolated enzymes are used to convert biological or other raw materials to products of greater values, as well as the design and use of reactors, fermenters, downstream processing, analytical and control equipment associated with biological manufacturing processes." Rochelle K. Seide & Frank A. Smith, *Intellectual Property Protection and Biotechnology*, N.Y. ST. B.J., May-June 1995, at 53 (citation omitted). *See also* Thomas E. Lovejoy, *Bugs, Plants and Progress*, N.Y. TIMES, May 28, 1995, § 4, at 11 (highlighting expansion of biotechnology, from environmental bioremediation to genetic engineering of organisms). "Biotechnology" and "biotech" are used where necessary for accuracy. The authors thank Pat Jones for suggesting this terminology.

2. The industry's national trade and lobbying association, the Biotechnology Industry Organization (BIO), has 520 members in 47 states. G. STEVEN BURILL & KENNETH B. LEE, JR., BIOTECH 94: LONG-TERM VALUE SHORT-TERM HURDLES 1 (1993) [hereinafter BIOTECH 94] (Ernst & Young's eighth annual report on biotech industry). In 1994, 1311 biotech companies were located in the United States, while 485 were located in Europe. G. STEVEN BURILL & KENNETH B. LEE, JR., BIOTECH 96: PURSUING SUSTAINABILITY 1, 39 (1995) [hereinafter BIOTECH 96]. The Japanese—expected to challenge the United States' accomplishments, outstrip the United States' investment in genotech, and even buy out huge numbers of United States companies—have not made major investments in the industry nor issued any major product approvals. G. STEVEN BURRILL & KENNETH B. LEE, JR., BIOTECH 95: REFORM, RESTRUCTURE, RENEWAL 21 (1994) [hereinafter BIOTECH 95]. *See generally* Robert A. Bohrer, *Foreword: What is Biotechnology and Why Devote a Law Review Symposium to Biotechnology Law?*, 55 U. PITT. L. REV. 607, 608 (1994) ("Outside the United States, . . . biotechnological research and development is being performed largely by traditional pharmaceutical and chemical companies either directly or in collaboration with United States [genotech companies].") (footnotes omitted). For discussion of the possibility that the genotechnology industry might migrate offshore, see BIOTECH 96, *supra* at 56. The biotech industry has more than 30 Food & Drug Administration (FDA)-approved drugs on the market as well as 637 approved biotech diagnostics. BIOTECH 94, *supra* at 35. Just 10 of these drugs generated world-wide revenues exceeding $4.5 billion in 1993. BIOTECH 94, *supra* at 30-31. The top 10 money-making drugs for 1995 are identified in *A Survey of Biotechnology and Genetics*, THE ECONOMIST, Feb. 25-Mar. 3, 1995, at 8 [hereinafter *Survey*].

3. BIOTECH 96, *supra* note 2, at 14; BIOTECH 95, *supra* note 2, at 15, 50; BIOTECH 94, *supra* note 2, at 5, 74; *see also infra* Appendix I (listing genotech drugs approved for market by FDA as of March 1995). Product sales for public biotech companies grew by 20% in 1994 and 21% in 1995. BIOTECH 96, *supra* note 2, at 9; BIOTECH 95, *supra* note 2, at 22.

4. Paul H. Silverman, *Commerce and Genetic Diagnostics*, HASTINGS CENTER REPORT, May-June 1995, at S16 (Special Supplement).

5. The huge potential of the gene diagnostic market was demonstrated by a recent survey in which 91% of breast cancer patients' immediate female relatives reported that they would want to be tested for genetic predisposition to the disease, were such a test to become availiable. C. Lerman et al., *Interest in genetic testing among first-degree relatives of breast cancer patients*, 57 AM. J. MED. GEN. 385-92 (1995).

6. Amgen, based in Thousand Oaks, California, is the largest and most successful biotech company in the world. *See, e.g.*, BIOTECH 96, *supra* note 2, at 70. In December 1994, it was one

may generate close to $1 billion in revenue per year.[7]

Advances in genotechnology have been made considerably faster than anticipated a decade ago.[8] The Human Genome Project, an international effort to map and sequence the genes on all twenty-three pairs of chromosomes,[9] is advancing more rapidly than originally predicted.[10] Innovations in computer technology that enhance the speed and precision of research and decrease

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of only six companies awarded a National Medal of Technology by the President and United States Department of Commerce.

7. Terry McDermott, *The Rarest Thing on Earth: The Story of an Elusive Blood Hormone, A Determined Group of Seattle Researchers and Biotechnology's Power and Promise*, SEATTLE TIMES, Dec. 18, 1994, at A1. Epogen, a hormone responsible for stimulating red blood cell production which was isolated almost one decade ago, has been on the market for five years. *Id.* Although the total amount produced and sold could fit within a bucket, epogen has generated $5 billion in sales. *Id.*; *cf.* Lawrence M. Fisher, *Biotech Discovery Announced by Firms*, DAILY NEWS OF L.A., June 17, 1994, at B3 (two genotech drugs, Erythropoietin and Granulocyte Colony Stimulating Factor, which stimulate red and white blood cell production respectively, have each generated more than $1 billion in sales worldwide, making them the most successful genotech products to date).

8. The following is a time-line of major discoveries and advances:

1953 James Watson and Francis Crick discover DNA's structure;

1966 Scientists elucidate the functional structure of genes—that they consist of groups of three molecules, located in strands of DNA, which provide the code for particular amino acids, the building blocks of proteins (*see infra* Section I.1);

1973 Stanford researchers are the first to clone genes;

1975 Harvard researchers are the first to isolate and clone a mammalian gene (a component of hemoglobin in rabbits);

1977 A human gene is cloned for the first time;

1988 Congress funds Human Genome Project (HGP);
FDA enacts accelerated regulatory process for products combatting terminal disease;

1989 A cystic fibrosis gene is identified and identification of other genes immediately follows;

1990 Work on the Human Genome Project, a commitment of $3 billion over 15 years, commences;
Dr. Venter introduces a method for sequencing human genes and distinguishing genes (just 3% of DNA) from junk DNA; First human gene therapy is introduced;

1992 Dr. Venter leaves NIH to set up The Institute for Genetic Research (TIGR);
Several thousand gene sequences are identified, and NIH files patent applications for them—thereby igniting international controversy;

1994 Merck supports a massive sequencing effort at Washington University;

1995 An estimated 85-90% of human genes are partially sequenced.

BIOTECH 96, *supra* note 2, at 60; John Carey, *The Gene Kings*, BUS. WK., May 8, 1995, at 72, 73. For an excellent overview of the accomplishments and health care potential of genotech, see *Survey*, *supra* note 2. Many of the incredible possibilities that may be realized in the near future are discussed in Gene Bylinsky, *Genetics: The Money Rush is On*, FORTUNE, May 30, 1994, at 94. Insights into the mechanisms behind human cancers, obtained in part through genotech, are explained in Webster K. Cavenee & Raymond L. White, *The Genetic Basis of Cancer*, SCI. AM., Mar. 1995, at 72.

9. JOSEPH LEVINE & DAVID SUZUKI, THE SECRET OF LIFE 30-31 (1993); *see infra* Section II.A.

10. *See, e.g.*, *Positional Cloning Approach Expedites Gene Hunts*, HUM. GENOME NEWS, Mar.-Apr. 1995, at 1-2; *U.S. Human Genome Project Updates Goals*, HUM. GENOME NEWS, Nov. 1993, at 1.

human error are accelerating the rate of progress.[11]

The promise, possibilities, and challenges of the genotech industry are many times greater than what is readily visible.[12] There are at least 5000 genetically-related diseases and conditions for which there are no cures.[13] Genotech-based advances in human health care will be as profound as those associated with anesthesia and antibiotics;[14] some may prove even more profound.[15] Diagnostics that identify faulty genetic sequences associated with cancers and other common diseases and therapeutics that counteract predispositions for disease should be available by the end of this century or early in the next, thereby injecting multiple billions of dollars into the industry.[16]

The business of genotechnology is built upon an idiosyncratic collection of alliances between academics, venture capitalists, for-profit and not-for-profit institutions, large federal agencies, multi-national pharmaceutical companies (pharmas), and small, entrepreneurial firms. While the accomplishments of the genotech industry are largely attributable to the private sector and academia, the federal government has deliberately and extensively fostered the industry's growth in an effort to improve the nation's health care capability. As discussed in detail in Section II, federal policy has played an important role in the unprecedented advances in the science of genotech and the almost immediate emergence of a genotech industry characterized by commercial alliances between the public and private sectors.

Unfortunately, federal policy regarding genotech has been grossly short-sighted. Rapid advances in genotech research and product development have not been accompanied by the legal and regulatory advancements necessary for responsible commercialization of genotechnologies. For example, the Food and Drug Administration (FDA) and Patent and Trademark Office (PTO) have

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11. *See, e.g.*, Ralph T. King Jr., *Gene Machines: An Eclectic Scientist Gives Biotechnology a Fast Assembly Line*, WALL ST. J., May 30, 1995, at A1, A5; *Positional Cloning Approach Expedites Gene Hunts*, *supra* note 10, at 1-2.

12. *See generally* BIOTECH 96, *supra* note 2 (pharma and genotech company contributions to human health have been profound); THE BOSTON CONSULTING GROUP, INC., THE CONTRIBUTION OF PHARMACEUTICAL COMPANIES: WHAT'S AT STAKE FOR AMERICA 65-67 (Sept. 1993) ("Biotechnology is a breakthrough in biological understanding that will eventually lead to a revolution in available disease treatments.").

13. Ralph Oman, *Biotech Patenting Issues Raise Ethical Concerns*, NAT'L L.J., May 8, 1995, at C42, C42.

14. *See* Lissa Morgenthaler, *Just What the Doctor Ordered*, BARRON'S, Sept. 20, 1993, at 10 ("Some scientists have hailed gene therapy . . . as the fourth great advance in health care, after sanitation, anesthesia and pharmaceuticals.").

15. *See generally infra* Section I.A. (addressing the status and importance of the industry).

16. *See* Carey, *supra* note 8, at 72, 78. *But see* Christine Gorman, *Has Gene Therapy Stalled?*, TIME, Oct. 9, 1995, at 62-63 (noting that while gene therapy holds extraordinary promise, enthusiasm and financial pressures may have caused a premature push to market that is sacrificing basic science and human safety for a quick return on investment).

begun only recently to adapt their review processes in a meaningful way to account for the unique risks and potentials for profit of genotechnologies. Neither state nor federal policymakers have acted to ensure that genotech commercialization proceeds responsibly within an appropriate regulatory and ethical framework. This failure, among other things, has allowed some commercial and academic laboratories to bypass regulatory and ethical quality controls in their efforts to commercialize gene tests predicting future health risks.[17]

The absence of a coherent and comprehensive federal policy has widened the gap between genotech's scientific and medical advances and the regulatory and legal mechanisms needed to ensure that genotechnologies are made available quickly *and* used responsibly and safely. The end result is an industry built upon inflated short-term expectations and subject to extremely variable investment cycles. As a result, financially vulnerable firms are rushing to commercialize emerging HGP technologies. Critics allege that scientific judgment is being sacrificed for quick profits.

The lack of an appropriate legal and regulatory infrastructure has created a growing danger that public misunderstandings of the genotechnologies and a few widely publicized failures could result in stop-gap policymaking rather than policymaking based on a thoughtful assessment of the risks and potential posed by genotech. This danger is increasing as more commercial applications of genotech are introduced into the healthcare market.

This Article will first present an overview of the genotech industry and how federal policy has shaped and continues to influence the science and business of genotech. Section I provides a brief summary of the basic scientific foundations and medical applications of genotech and discusses the nature of the industry. Section II describes the federal government's past and present involvement in the industry.

Section III proposes policy changes that would promote the government's interests in genotech development, yet take into consideration the risks and ethical issues presented by these novel technologies.[18] We suggest that the federal government has been too hasty and short-sighted in its support of the

17. Such was the conclusion reached by an HGP task force in a report released at the October 1995 annual meeting of the American Society of Human Genetics. Richard Saltus, *Survey of Labs, New Tests Concerns Genetics Specialists*, BOSTON GLOBE, Oct. 28, 1995, at 14. In a report issued in early 1995, the Institute of Medicine's Committee on Assessing Genetic Risks concluded that as genetic screening becomes more widespread, public policy needs may quite possibly outrun the ethical and regulatory standards in place. *See* ASSESSING GENETIC RISKS 247-82 (Lori B. Andrews et al. eds., 1994).

18. Many of the serious implications of these technologies are identified and mentioned briefly throughout this Article, but are not fully explored; one of the most obvious is who will pay for patient use of the technologies. Such questions require comprehensive and careful treatment, both by policymakers and scholars, which is beyond the scope of this Article.

industry, thereby giving rise to a "false start" for the genotech industry.[19] While federal policy has facilitated the accelerating scientific accomplishments of the industry, policymakers and drug regulators have begun only recently to respond to the novelty of genotechnologies and the unique issues they raise. The delay is underscored by the fact that the advancement of genotechnology and many of these issues have been foreseeable for years.

Section III also addresses another aspect of this "false start." Ironically, in the absence of the legal and regulatory infrastructure necessary to commercialize genotechnologies, the scientific success of HGP is escalating the potential for irresponsible applications of genotechnologies and reactionary public policymaking. Investors in genotechnology have lofty expectations, but are notoriously short-sighted and jittery. The absence of policymaking addressing the social and ethical implications of genotech capabilities is becoming more ominous as those capabilities continue to advance and expand, and genotech-based products reach commerce. Without the appropriate legal and regulatory infrastructure, the overall impact of federal policy on the genotech industry may be to delay and impede the marketing of genotech diagnostics and therapeutics, thereby defeating the central objective of HGP. We do not propose that genotechnologies be made generally available before adequate policy safeguards are in place and the efficacy of the technologies is fully evaluated. We do, however, suggest that any regulatory policies that slow the availability of these technologies should be carefully and deliberately considered and implemented. A central premise of this Article is that delaying the introduction of genotechnologies due to lack of reasoned policy decisions is irresponsible.

Accordingly, Section III sets forth proposals to improve federal policy. It focuses primarily on two things: (1) creating a more certain legal environment to reduce investment volatility; and (2) adjusting federal processes to encourage efficient yet prudent review of genotechnologies, with the hope that these proposals will help to bring genotech products to market in a manner that is both timely and responsible.

I. The Accomplishments and Promise of Genotechnology

It is no coincidence that the great majority of the world's genotech companies are located within the United States.[20] As discussed below, although the industry's accomplishments are very much attributable to private enterprise and academic excellence, the United States government has been

19. *Cf.* Gorman, *supra* note 16, at 62-63 (suggesting that the rush to develop and commercialize gene therapies may have misdirected efforts away from necessary, basic scientific research).

20. *See supra* note 2 and accompanying text.

deliberately fostering the underlying science and growth of the genotech industry. As a result, the industry, although perhaps still nascent in terms of actual commercialization of diagnostics and therapeutics, has attained a substantial domestic and international presence within a remarkably brief period of time.[21] For example, Genentech, Inc., one of the most successful genotech companies to date, was founded in 1976 with a $1000 investment.[22] In 1994, the company generated $795.4 million in revenue.[23]

The genotech industry has realized the vast majority of its accomplishments within just the last five years. Consider that five years ago, less than five percent of all human genes had been identified. Now, DNA sequences representing parts of eighty-five to ninety percent of all genes have been identified, and the scientific community is rapidly matching these sequences to gene functions.[24] The following is a discussion of the present importance of the industry and the federal policy that has contributed to the industry's accomplishments.

A. *The Science and Medicine of Genotech*

Medical science is moving from a century dominated by physical science into one dominated by biological science.[25] Health care and drug development are undergoing a fundamental change in methodology. In the past, medical care was generally directed towards immunizing against disease and suppressing the symptoms of those diseases that could not be prevented. Now, however, medical researchers are attempting to understand the biochemical intricacies which cause health conditions.[26] As they come to understand the biochemical functions of genes, scientists will be able to identify and correct the specific defects that cause illnesses.[27] Thus, rather than just treating or supressing

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21. *Id.*

22. McDermott, *supra* note 7, at A1.

23. Steve Ginsberg, *Genentech Buys Chevron Land for Expansion*, SAN. FRAN. BUS. TIMES, Sept. 22, 1995, at 6. In the third quarter of 1995, Genentech generated $40.2 million in profit, compared to $33.6 million in the third quarter of 1994. *Third-Quarter 1995 Profits for 711 Companies*, WALL ST. J., Nov. 6, 1995, at A8.

24. Carey, *supra* note 8, at 73. However, less than 5% of the genetic code has been sequenced fully, meaning that the precise nucleotide composition of more than 95% of the human genome is yet to be determined. Mariette DiChristina, *Unraveling the Mystery of Life*, BOSTONIA, Fall 1995, at 16.

25. *See generally* BOSTON CONSULTING GROUP, INC., *supra* note 12, at 65.

26. This emphasis on fully understanding and influencing the impact of biochemistry on human health has been coined "Darwinian" or "evolutionary" medicine. *See* Terry McDermott, *Darwinian Medicine: It's a War Out There and Margie Porfet, a Leading Theorist in a New Science, Thinks the Human Body Does Some Pretty Weird Things*, SEATTLE TIMES, July 31, 1994, at 10.

27. *See* Craig W. Johnson, *Recent Developments in Venture Capital Financing for Biotechnology Companies*, *in* ALI-ABA COURSE OF STUDY, BIOTECHNOLOGY: BUS., L. AND REG., Nov. 18, 1993, *available in* WESTLAW, C886 ALI-ABA 1, 4. ("[A]s the collective

symptoms, the genotech industry aims to identify and attack the root causes of disease.

Medical applications of genotech are already moving rapidly towards the healthcare marketplace. Biotech-related investigative new drug applications (INDs) now represent forty-five percent of all INDs.[28] Approximately 2000 biologically-derived drugs are in developmental stages and over 494 products are in human clinical trials, the last prerequisite for seeking full marketing approval from the FDA.[29] Approximately 120 of these drugs are in Phase III advanced clinical trials, a stage reached by fewer than twenty percent of all drugs entering human trials.[30] Genotech products are likely to reach market quickly over the next several years because multinational pharmaceuticals have recently begun investing money and other resources into genotech companies,[31] which in turn has helped renew investor confidence in the industry.[32]

1. *The Science of Genotech*

The human body consists of an estimated 60 to 100 trillion cells, each of which, with a few exceptions, has a full complement of twenty-three pairs of chromosomes containing 60,000 to 100,000 genes.[33] In terms of scale, if the human cell is equated to the earth, then the cell's nucleus is the equivalent of a continent, each chromosome the equivalent of a state, individual molecules of chromosomal DNA the equivalents of cities, genes the equivalents of

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understanding of the body's chemical mechanisms becomes clearer (the human genome project is an example), new approaches to drug development to promote or retard these mechanisms for therapeutic purposes becomes more obvious.") The accomplishments of the genotech industry also have redirected the course of the research and development efforts of pharmaceutical companies. *See* Carey, *supra* note 8, at 76-77 (noting that, whereas drugmakers have had to test thousands of chemicals to find one that alleviates a particular medical symptom, they now have begun to understand the underlying biology and as a result narrow their research to find proteins or other molecules that block or activate particular biochemical pathways).

28. BIOTECH 94, *supra* note 2, at 38.

29. BIOTECH 96, *supra* note 2, at 23 (relying upon Goldman Sachs data); *Swiss Betting Big On Biotechnology*, ORLANDO SENTINEL, Nov. 30, 1995, at B1.

30. BIOTECH 96, *supra* note 2, at 23-24. The drug-approval process is discussed *infra* at Section II.D.1.

31. Bylinsky, *supra* note 8, at 95, 108; Lawrence M. Fisher, *Gene Project is Already Big Business Profit Potential Heavily Based on Public Research*, SAN JOSE MERCURY NEWS, Jan. 30, 1994, at 9A (expecting products to be in the marketplace by 1998-99).

32. Ellie McCormack, *Biotech Stocks Regain Health: Share Prices are Rising Amid Flood of Secondary Offerings*, BOSTON BUS. J., Aug. 18-24, 1995, at 1, 28; *see also* BIOTECH 96, *supra* note 2, at 9-10.

33. LEVINE & SUZUKI, *supra* note 9, at 67; Michael Kirby, *The Human Genome Project—Promise and Problems*, 11 J. CONTEMP. HEALTH L. & POL'Y 1, 8 (Fall 1994); Carey, *supra* note 8, at 74. *But see* LEVINE & SUZUKI, *supra* note 9, at 67 ("[T]he oft-quoted estimates of 100,000 genes are relatively arbitrary, and may well understate our genetic complexity.").

specific streets, and the nucleotides of which the genes are comprised the equivalents of houses on those streets.[34]

Each gene is a unique sequence of DNA that, when active, encodes a protein or protein fragment.[35] Each protein, in turn, consists of a unique combination of the twenty amino acids that comprise all proteins.[36] While each cell contains the entire complement of an individual's chromosomes, different genes are active in different cell types and at different times, so cells differ in protein content and perform different functions.[37] This great variety of composition and distribution allows proteins to perform the extraordinary assortment of tasks that together give living organisms their structural forms and capacities for action.

A person's visible characteristics (his or her "phenotype") are thus controlled by his or her genetic makeup ("genotype") and environmental factors.[38] By instructing cells how and when to make proteins, genes help determine, for example, whether we are tall or short, good at hitting home runs, predisposed to developing colon or breast cancer, likely to produce healthy children,[39] or destined to be stricken with Huntington's disease.[40] Scientists can map the chromosomes—that is, identify where genes are situated precisely within the universe of the human genome—because each gene occupies a particular spot on a particular chromosome.[41] Recently and for the first time, scientists deciphered the entire DNA sequence—a chain of 1,830,121 DNA bases—of a living organism, *Hemophilus influenza*.[42] The long-term objective of HGP is to do the same for the human body.[43] Scientists have already sequenced fragments of eighty-five to ninety percent of the

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34. This analogy, although slightly altered, is borrowed from Bylinsky, *supra* note 8, at 96.

35. The DNA of the 23 pairs of chromosomes is made up of about 3 billion nucleotide pairs, of which only about 3% are thought to comprise genes. LEVINE & SUZUKI, *supra* note 9, at 18, 28; Bylinsky, *supra* note 8, at 100; Carey, *supra* note 8, at 74-75. Each nucleotide contains one of four elements (or "bases") that comprise the fundamental four-letter molecular code. LEVINE & SUZUKI, *supra* note 9, at 18-19. Even a small gene contains 3,000 base pairs, and genes can be much larger. *Id.* at 18.

36. LEVINE & SUZUKI, *supra* note 9, at 19; Christopher A. Michaels, *Biotechnology and the Requirement for Utility in Patent Law*, 76 J. PAT. & TRADEMARK OFF. SOC'Y 247, 250 (1994).

37. LEVINE & SUZUKI, *supra* note 9, at 11, 64-66.

38. *See, e.g., id.* at 220-251.

39. For a discussion of prenatal genetic screening and related ethical issues, see Michael J. Malinowski, *Coming Into Being: Law, Ethics, and the Practice of Prenatal Genetic Screening*, 45 HASTINGS L.J. 1435 (1994).

40. Seide & Smith, *supra* note 1, at 53-54; Carey, *supra* note 8, at 72.

41. Oman, *supra* note 13, at C42; *see also* LEVINE & SUZUKI, *supra* note 9, at 28-29.

42. *Scientists Decode a DNA Sequence*, BOSTON GLOBE, May 26, 1995, at 10.

43. LEVINE & SUZUKI, *supra* note 9, at 30-31; *see also* Carey, *supra* note 8, at 77 ("Experts believe a database of all human genes must be laden with clues to previously unknown biochemical pathways that could be manipulated to treat or prevent the disease.").

estimated 100,000 genes.[44] It is virtually certain that researchers will have sequenced all human genes and know the amino acid composition of all human proteins by the year 2010.[45]

Mapping and sequencing genes is frequently only the beginning of a researcher's task, as is underscored by the fact that the human and chimpanzee genomes differ in DNA content by only about 1.5 percent.[46] The real challenge is identifying what genes do and how they contribute to phenotypic characteristics, especially those associated with disease.[47] Generally, scientists must determine what protein(s) a gene sequence (or combination of sequences) encodes and then identify and trace the gene's role in cellular processes.[48] The task is even more difficult when the subject of research is a condition, like asthma or diabetes, that may result from multiple gene defects on more than one chromosome.[49]

Nonetheless, scientists have already identified genetic defects associated with approximately 200 conditions, including Huntington's disease, cystic fibrosis, several cancers, and Alzheimer's disease.[50] In just the last six months, scientists have isolated and confirmed genetic links to obesity in mice,[51] found an inherited genetic mutation in humans that appears to cause

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44. Carey, *supra* note 8, at 74.

45. *See Survey*, *supra* note 2, at S4 ("It is entirely conceivable that, by the end of the century, scientists will know the true names [sequences] of all the proteins the human body uses; it is inconceivable that the names should not be known by 2010. . . . Once all the genes have been cloned, the raw stuff of all human inheritance will be laid bare. The implications of that go far beyond the fortunes of a bunch of biotechnology companies.").

46. Bylinsky, *supra* note 8, at 96. Even fruit flies make proteins that are identical or similar to those made by human genes. *Id.* The genetic simililarities between humans, chimpanzees, and fruit flies suggest just how subtle, complex, and difficult to uncover are the connections between genotype and phenotype. Yet interspecies genetic similarities are essential to the study of human genetics. *See generally* LEVINE & SUZUKI, *supra* note 9, at 21-33. The vast majority of the techniques used in genotech research were developed for research on bacteria and viruses. *Id.*

47. For examples of how such puzzles have been solved by researchers, see, for example, *Survey*, *supra* note 2, at S6; McDermott, *supra* note 7, at A1.

48. *See, e.g.*, Bylinsky, *supra* note 8, at 99-101.

49. Such conditions are termed "polygenic" or "multifactorial." *Id.* at 100; Malinowski, *supra* note 39, at 1440.

50. Morgenthaler, *supra* note 14, at 11; Richard Saltus, *Early Alzheimer's: Do You Want to Know?*, BOSTON GLOBE, July 3, 1995, at 39, 43 [hereinafter Saltus, *Do You Want to Know?*]. Researchers have identified a gene that causes a form of early-onset, familial Alzheimer's thought to afflict approximately 200,000 of the four million who have Alzheimer's. Richard Saltus, *Gene that Causes Early Alzheimer's is Reported Found*, BOSTON GLOBE, June 29, 1995, at 1, 17. The most common form of Alzheimer's, which accounts for about 85% of all cases, is believed to result from a combination of genetic predispositions and environmental factors. *Id.*; Saltus, *Do You Want to Know?*, *supra*.

51. Richard Saltus, *Weight Loss Hormone Reported*, BOSTON GLOBE, July 27, 1995, at 1, 10. Scientists isolated a hormone, called "leptin" and produced by an "obesity" gene identified last year, that controls obesity in both "obesity"-mutant and normal mice. *Id.* Researchers also identified a second gene, "tub," associated with obesity in mice. *Id.* Some scientists are skeptical, however, that the discovery of these genes in mice will result in products for people any time

a propensity for adult-onset diabetes and obesity,[52] and shown that a gene thought to be involved in Alzheimer's disease may serve as a marker for life expectancy.[53] Furthermore, discoveries from research targeting specific diseases and conditions are elucidating entirely different diseases and conditions. The search for a vaccine against HIV, for example, may benefit cancer and tuberculosis patients;[54] deadly microbes like the Ebola virus may eventually be defeated by means of discoveries made in work on other viral systems.[55]

2. *Transforming Science into Diagnostics and Therapeutics*

The genotech industry has come a long way since the introduction of the first medical genotech product, a version of insulin.[56] The most important contribution from the patient perspective is the advent of gene therapy.[57] Gene therapy,[58] albeit still in nascent form, is a reality which has been in existence since 1990.[59] In fact, as of 1993, well over 100 gene therapy procedures had

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soon. *See* Richard Saltus, *Some Scientists Skeptical of a Cure*, BOSTON GLOBE, July 28, 1995, at 3.

52. Alison Bass, *Genetic Mutation, Obesity: A New Link Area Is Related to Inadequate Calorie Burning*, BOSTON GLOBE, Aug.10, 1995, at 4.

53. Jerry E. Bishop, *A Gene Gives a Hint Of How Long a Person Might Hope to Live*, WALL ST. J., Oct. 19, 1995, at 1, 14.

54. Many therapeutic vaccines are being tested in people with AIDS and, if successful, could lead to treatments for other viral infections, cancer, and a variety of immune deficiencies. *See Aids Vaccine Effort Offers Unseen Benefits*, ORLANDO SENTINEL, Mar.21, 1993, at G7. However, several clinical studies of vaccines have had very dissappointing results. *See, e.g.*, John Crewdson, *Hope Fades for AIDS Vaccine Soon: Results of Tests Dissappointing*, CHICAGO TRIBUNE, Nov.12, 1995, at 1 (prospects for AIDS vaccine by turn of century dimmed further after failure of gp120 vaccine to protect high-risk volunteers from contracting HIV; researchers' estimates of when a successful vaccine will be found range from five to 25 years). There is also concern that the experimental vaccine will be ineffective against other strains of HIV which have slightly altered surface proteins. Carey, *supra* note 8, at 77.

55. An outbreak of the Ebola virus killed over 200 people in Zaire earlier this year. *Science Briefs: Army Joins Hunt for Ebola's Source*, BOSTON GLOBE, June 12, 1995, at 29; *see generally* RICHARD PRESTON, THE HOT ZONE (1994).

56. *Survey*, *supra* note 8, at S5; *see generally* Appendix I.

57. See Lawrence M. Fisher, *Bottling the Stuff of Dreams*, N.Y. TIMES, June 1, 1995, at D1 (stating that companies developing these technologies are "edging closer to unlocking the therapy's vast potential to correct genetic defects and, in theory at least, treat almost every disease known to man"). *But see* Gorman, *supra* note 16 (contending that safe and effective gene therapy is a long way off and quoting the NIH's Dr. Harold Varmus, who is concerned that government is not getting its money's worth from its gene therapy investment: "My intuition tells me that we need to emphasize more basic aspects of gene therapy research.").

58. "Gene therapy involves inserting genes into a cell of an individual to compensate for a deficiency or to give the cell a new characteristic." Daniel Sutherland, *New Area Company to Work on Gene Therapy*, WASH. POST., Mar. 4, 1993, at D12.

59. Oman, *supra* note 13, at C42 ("On September 14, 1990, 4-year-old Ashanti DeSilva—who had been born without a working immune system resulting from a rare disorder called SCID, or sever combined immune deficiency—was given new genes to correct the defect.

been approved for and were in clinical trials in the United States and Europe.[60] One of the newest products to reach the market, administered through inhalers, is a treatment for cystic fibrosis, a disease afflicting 30,000 Americans.[61]

The general premise of gene therapy is that genes contain the recipes for proteins, and defective genes make defective proteins.[62] Among the various approaches to and technologies associated with gene therapy,[63] one methodology (*in vivo*) is to isolate, purify, and introduce the desired gene into the body, and then into cells' genomes, by means of a vector, such as an inactive virus with a prowess for penetrating cells; another approach (*ex vivo*) involves introducing the gene into cells that have been removed from the

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. . . This was the first time gene therapy had been administered to a human in an attempt to cure disease. Ashanti, now eight years old, is able to attend school and lead a normal childhood.") (footnote omitted). In October 1995, scientists declared this first gene therapy a success. *See* Dolores Kong, *Study: First Gene Therapy a Success*, BOSTON GLOBE, Oct. 20, 1995, at 3.

60. Morgenthaler, *supra* note 14, at 10.

61. Natalie Angier, *Gene Therapy Begins for Fatal Lung Disease*, N.Y. TIMES, Apr. 20, 1993, at C5 (reporting on the therapy); Marilyn Chase, *Genentech's Cystic Fibrosis Treatment is Unanimously Cleared by the FDA Panel*, WALL ST. J., Aug. 10, 1993, at B6. The search for the cystic fibrosis gene cost $150 million and took three years. John Carey, *Gene Hunters Go for Big Score*, BUS. WK., Aug. 16, 1993, at 98. Analysts estimate that Genentech's treatment, Fyurmean DNase, will generate $300 million in annual revenues by 1996 and up to $500 million worldwide; however, Genentech's window of opportunity to recoup its investment may not remain open for long: gene therapy has "potential to cure CF, thereby making DNase obsolete." Joan Hamilton, *A Star Drug is Born*, BUS. WK., Aug. 23, 1993, at 66. *But see* Jerry E. Bishop, *Biotechnology: . . . but Trials Deflate Hope for Therapies*, WALL ST. J., Sept. 28, 1995, at B1 (reporting failure of attempt to use genetically engineered common cold virus to insert normal gene into CF patients).

62. *See* LEVINE & SUZUKI, *supra* note 9, at 192-93, 195 (gene therapy is human genetic engineering aimed at correcting or replacing defective genes); Bylinsky, *supra* note 8, at 108 (objective of gene therapy is to introduce new genes into cells to restore production of proteins that, when missing or mutated, cause disease); Morgenthaler, *supra* note 14, at 10 (objective of gene therapy is to get the necessary protein to the appropriate sites within cells without the problems associated with conventional drugs).

63. Carey, *supra* note 8, at 75. HGS and its affiliates are sequencing DNA fragments (called cDNA) from almost all human genes with the objective of establishing a database resource for the research and development of therapies. *Id.* at 76. The data base allows researchers to identify human analogs of genes identified in yeast, bacteria, or other research organisms, and vice versa. *See, e.g., id.* (In December, 1993, two Johns Hopkins University oncologists "were racing to catch up with rivals at Harvard and the University of Vermont in a hunt for the gene that, when flawed, causes inherited colon cancer. They suspected that the gene normally fixes errors made when cells copy DNA during cell division and had in hand such a gene from yeast. So, in what many see as a vindication of the cDNA approach, they agreed to cede product rights [to HGS] in return for access to HGS's database. In minutes, they found the human version."). Other companies are taking a more focused approach. For example, Myriad Genetics, Sequana, Mercator and Millennium are studying families with high incidences of diseases such as diabetes and cancer to identify the underlying genetic mechanisms. *Id.* at 78. Sequana Therapeutics is searching family histories and HMO data for genes associated with hypertension, obesity, and asthma. *Id.* at 76.

patient and then putting the cells back into the body.[64] Genes may also be used, as is now most common, to manufacture proteins in bulk as pharmaceutical drugs or other useful compounds to cure human disease.[65] A major objective of the industry is to develop an approach to deliver corrective genes to the nuclei of cells that is administered, packaged and sold like other drugs.[66] The industry's products have been grouped as diagnostics; gene therapeutics based upon the introduction of new genes; gene regulators which function by replacing command sequences; protein therapeutics which are medicinal proteins produced in laboratories; and small molecule drugs ("bio molecules") administered by injecting proteins directly into the blood or in pill form, possible because these small molecules are able to pass through the stomach lining.[67]

Much of the genotech industry's efforts and the investment of pharmas are concentrated on cancer-related drugs.[68] The resulting drugs and diagnostic

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64. *See, e.g.*, LEVINE & SUZUKI, *supra* note 9, at 208-15; Fisher, *supra* note 57, at D1; *cf.* Bishop *supra* note 61 (noting failure of cystic fibrosis and muscular dystrophy gene therapy experiments); Robert Langreth, *Gene-Based Vaccines Ride Directly to Cells on Backs of Bacteria, Delivery System Has Promise for Bringing "Naked DNA" to Hard-to-Reach Organs*, WALL ST. J., Oct. 13, 1995, at B3 ("Researchers cautioned that the approach has been tried only in animal experiments and it will likely be several years before its potential for use in humans is known."). This virus-delivery approach does, however, carry some risk—both of infecting the patient with the virus and of rejection, since viruses tend to trigger the cell's immunity mechanisms. *See* Michael Waldholz, *To Fight Disease, Researcher Reforms Cold Virus's Evil Ways*, WALL ST. J., Jan. 18, 1994, at B1. For a discussion of another approach to gene therapy delivery, which makes use of liposomes, see Judy Foreman, *Gene Therapy System Aims to Restore Youthful Hair*, BOSTON GLOBE, June 30, 1995, at 1, 4. Liposomes, applied to skin, are able to slip easily through cell membranes, and this approach is being used in research on gene therapy to restore youthful hair. *Id.*

65. Fisher, *supra* note 57, at D1; Oman, *supra* note 13, at C42.

66. *See* Fisher, *supra* note 57, at D1 (stating that at present most genetic therapies are administered *ex vivo* and the major obstacle is developing the means to administer them *in vivo*, meaning to introduce them into and have them become a lasting part of the cell function). *But see* Bishop, *supra* note 61.

67. All of these technologies are discussed in Bylinsky, *supra* note 8, at 107-08. The technologies are often grouped by the industry into the following areas of concentration: bio molecules; drug delivery; drug design; drug development; disease-specific drug discovery; immunotherapy; living cell therapy; monoclonal antibodies; and proteins. BIOTECH 95, *supra* note 2, at 18.

68. *See generally* Webster K. Cavenee & Raymond L. White, *The Genetic Basis of Cancer*, SCI. AM., Mar. 1995, at 72-81; James Flanigan, *What Ails the Drug Industry Has Little to Do With Politics*, L.A. TIMES, May 25, 1994, at 72-81. For example, Matritech has sought FDA approval for a protein-based bladder cancer test and is developing similar tests for breast, cervical, colorectal, and prostate cancers. *Maritech Asks FDA to Approve Bladder Cancer Test*, NEWS RELEASE (Maritech Corporation), Nov. 9, 1994. Genentech Inc. and Zymogenetics Corporation have announced the discovery of a hormone, thrombopoietin, that stimulates the production of blood-clotting platelet cells, which are destroyed by chemotherapy and radiation cancer treatments; the world-wide market for the hormone is estimated at $1 billion. Fisher, *supra* note 7, at B3. Immunex Corporation and Genetics Institute Inc. have other platelet-stimulating drugs in clinical trials. *Id.*

capabilities are likely to be at the forefront of the forthcoming generation of genotech products.[69] For example, researchers claim to have found a genetic marker for colon cancer, the second leading cause of cancer-related deaths in the United States.[70] An individual in whom the marker is detected may have an astonishing ninety-five percent chance of developing the cancer.[71]

The diagnostic prospects associated with "genotyping" offer perhaps the most immediate and significant possibilities. In its simplest form, genotyping technology is diagnostic capability. Eventually, it will enable health care providers, pharmas, and genotech companies to determine which drugs and therapies will work on individual patients—thereby eliminating wasteful drug consumption, lost treatment time, unnecessary side effects, and some costs.[72] In an era of reductions in health care financing, pharmas and genotech companies will be better able to assess their markets and, therefore, enhance their efficiency.[73] The direct implication of this technology for individuals is that one's genetic profile "will become an indispensable part of the medication [he or she] might be prescribed."[74] Once this genotyping technology is fully advanced, health care providers may be able to design drugs on demand that are fitted to target each person's biochemical needs.[75]

3. *The Drug-Development Time Lag*

Considering the youth of the genotech industry and the fact that the time-frame required for an idea to evolve into a marketable drug or other product is generally ten or more years, it is extraordinary that an entire generation of

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69. Investors are also seeking out products close to reaching market. *See* Lisa Eckelbecker, *Biotech's Long, Hot Summer*, WORC. TEL. & GAZETTE, Sept. 3, 1990, at E1, E2 (stating that "biotech investors want products close to market").

70. Kirby, *supra* note 33, at 12.

71. *Id.* Recently, scientists determined that tomerase, an enzyme which repairs the ends of chromosomes, is active in many cancers, thereby making it a prime R&D target for developers of both diagnostics and therapeutics. *Scientists Report "Immortality" Enzyme in Many Cancers*, BOSTON GLOBE, Dec. 23, 1994, at 3.

72. *See Survey*, *supra* note 2, at 14. "Pharmocogenetics" is the name given this emerging field that seeks to dissect diseases genetically in order to match diagnoses and treatments more effectively. *Id.*

73. *See id.* at 14-15; *cf.* Michael Schrage, *Drug Merger Frenzy Dampening Confidence in Future*, BOSTON GLOBE, Feb. 5, 1995, at 32 (arguing that the industry offers investment opportunities which are being missed).

74. Schrage, *supra* note 73.

75. Leslie Helm, *"Grind and Find" Robots, VDTs May Be the RX for New Pharmaceuticals*, L.A.TIMES, Nov.9, 1994, at D1. The methodology is that, "[f]irst, the objective is to find a protein, or 'receptor,' that plays a key role in a disease. Once a receptor is found, the task is then to find a compound that will attach itself to the receptor and either disable the receptor if it has harmful functions or activate it if it has a positive role. Think of the receptor as the lock that must be opened or closed for treatment and the drug as the key that must be found." *Id.*

novel drugs is already visible. Nonetheless, while the underlying science has proceeded more quickly than expected, the commercialization of genotech has been much slower and more expensive than anticipated due in part to the regulatory challenge of obtaining approval from the FDA.[76] Many genotech firms and investors may have assumed, incorrectly in retrospect, that the FDA would be quicker to approve technologies based on more "natural," biologically-derived molecules.[77] Firms overlooked the fact that genotech products are different than the products that FDA is accustomed to reviewing. In other words, what sets genotechnologies apart from traditional technologies and gives rise to their potential has held them back during some steps of the FDA process. The companies that arrive first at the FDA with proposed therapeutics and diagnostics in hand have found that the FDA process, while time-consuming, uncertain, and expensive under the best of circumstances, may be prohibitively so when applied to truly novel technologies. As "firstcomers," these companies bear the burden of designing and proposing adequate testing protocols and convincing regulators that both the protocols and the resulting data are adequate.

Since genotech companies lack established product lines, they must live off their capital while attempting to develop products, conduct trials, and get products to market.[78] The "burn rate" (the extent to which capital is exhausted on research and development (R&D) before profits from products are generated) in the genotech industry has been much higher than was anticipated in the 1980s.[79] Ernst & Young has estimated that, as of late 1994, one-half of the 132 publicly held biotech companies did not have enough capital to survive two more years.[80] During 1995, the overall survival index for the industry dropped from twenty-five months in 1994 to just sixteen months.[81] Such financial pressure has resulted in a race to push products through the FDA approval process before bank accounts are depleted, credit is tapped, and potential investors have lost interest.

Although the investment appeal of genotech has returned recently,[82] the investment cycles for the industry have been relatively brief and unquestionably extreme.[83] Moreover, federal grants for scientific research and development, traditionally a major source of funding for genotech efforts, appear to be at

76. BIOTECH 96, *supra* note 2, at 11; *see also infra* notes 239-241 and accompanying text.
77. BIOTECH 96, *supra* note 2, at 11.
78. BIOTECH 95, *supra* note 2, at 54.
79. *Id.* at 30-31.
80. *Id.* at 54.
81. BIOTECH 96, *supra* note 2, at 15.
82. *See supra* note 32.
83. *See supra* note 78.

the top of Congress' budget-cutting agenda.[84] Although it appears that a federal trust fund will be established to finance scientific research and NIH funding is being spared, there is no guarantee that these funds will escape congressional budget cuts in the future.[85]

In part, the problem the genotech industry is facing is familiar, as most new industries are confronted with some version of it. But the problem and its consequences have been exaggerated and intensified in the context of the genotech industry. The virtually unconditional support for genotech research, accompanied by international cooperation and competition, have resulted in a surge in technological advancement and given rise to a multi-billion-dollar, international industry in record time. Early success built tremendous expectations,[86] and the result is a hyper-sensitive market especially responsive to disappointments.[87]

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84. *See* Troy Goodman, *Should the Labs Get Hit?*, U.S. NEWS & WORLD REP., Nov. 6, 1995, at 83 ("Some of the most sweeping budget cuts considered this year have focused on science."); Charles Petit, *Huge Cuts on Horizon For Science: U.S. Spending Could Drop One-Third by the Year 2000*, S.F. CHRON., Aug. 29, 1995, at A5 (while cuts in science spending planned for many other agencies, the budget proposal would increase spending for medical research at NIH); *infra* Section I.B.

85. *See* Petit, *supra* note 84, at A5.

86. "In the past, some biotech companies, eager to obtain financing, often made broad claims regarding their product's futures—heralding cures for cancer or AIDS, for example. These companies often rushed products with large market indications through early clinical development and into Phase III in order to reap Wall Street's rewards—too often running into clinical disappointments." BIOTECH 95, *supra* note 2, at 38-39. The impact of such disappointments on the value of stock is direct and substantial: "Stocks like Synergyn, that once traded for as much as 60, have sunk to below 5 . . . . Furthermore, of about 300 biotech companies, only 14 have operating earnings." Herb Greenberg, *Biotech Babble—Is the Worst Finally Over?*, S.F. CHRON., July 25, 1994, at D1. At least one commentator has attributed these inflated expectations to genotech CEOs: "That the CEOs of these major biotechnology/pharmaceutical firms have little or no relevant scientific training in the technologies that drive their companies may in part account for the industry's exaggerated claims and failure to show leadership in research and development." Silverman, *supra* note 4, at S16. An alternative explanation is that "the capital markets were operating under the fallacious assumption that, because biotechnology dealt with molecules that were natural, biotech's products would be safer than traditional pharmaceuticals and would get through the FDA regulatory process faster." BIOTECH 96, *supra* note 2, at 11.

87. *See* Gorman, *supra* note 16, at 63; *infra* Section I.B. Consider the investment market's reaction to the announcement of Biogen, Inc., one of the first genotech companies to realize operating earnings, that it was abandoning development of hirulog, an experimental anticlotting drug. (The drug was effective, but cost seventeen times as much as the existing anticlotting drug; *see also* Ronald Rosenberg, *Biogen Lost a Drug, Kept its Health, Reputation*, BOSTON GLOBE, Nov. 20, 1994, at A1-2.) The company's stock price dropped 25% within a few days of the announcement and a flurry of class-action shareholder suits soon followed. *See, e.g.*, Lazar v. Biogen, Inc., et al., No. 94-12177PBS (D. Mass., filed Nov. 2, 1994) (representative of more than ten such complaints); Tom Schmitz, *High-Tech Heart Drug Gets Tiny Edge in Study*, SAN JOSE MERCURY NEWS, May 1, 1993, at 1A (reporting Genentech's experience with TPA, an anti-clotting enzyme that is somewhat more effective than an already-commercialized counterpart but costs five times as much); *cf.* Ronald Rosenberg, *More Woes Ahead for Biotech*, BOSTON GLOBE, Jan. 3, 1995, at 61 [hereinafter Rosenberg, *More Woes*] ("In the short history of commercial biotechnology, 1994 will be remembered as one of the bleakest years. Only one new biotechnology

When evaluating the industry, the inevitable drug-development time lag should not detract from the extraordinary technological accomplishments. Within the next year or two, some of the industry's most promising technologies will go into production.[88]

B. *The Genotechnology Industry: Shifting Alliances and the Impact of Federal Policy on Industry Structure*

The remarkable advancement of genotechnology during the last five years is attributable to both scientific advances and aggressive entrepreneurialism.[89] While the genotech industry began as pure science, concentrated in academia and aided by federal research grants and technology transfers, a myriad of discoveries with commercial potential enabled the industry to attract venture capital financing and, more recently, pharma funding. Pharma involvement has renewed general investment confidence in the industry, and small, speculative, independent genotech firms have largely been replaced by consolidated entities.[90]

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drug earned Federal Food and Drug Administration approval."); Daniel Sutherland, *Amgen to Buy Faltering Synergen for $240 Million*, WASH. POST, Nov. 19, 1994, at D1 ("The biotech industry . . . was a favorite for venture capital in the 1980s. But many of the promised products have proven far more difficult to make than expected, or have failed tests run by the Food and Drug Administration.").

88. *See* Tina Cassidy, *Biotech the Real Estate Decision*, BOSTON GLOBE, Feb. 5, 1995, at A13; *supra* note 31.

89. *See* Michael Malinowski, *Bringing Human Genome-Related Biotechnology to Market: A Matter of Survival*, THE HEALTH LAWYER, Early Spring 1995, at 8, 8.

90. *See* BIOTECH 95, *supra* note 2, at 22; *infra* note 254 (addressing CRO model). Organizational strategy has shifted from the original models—fully integrated pharmaceutical company (FIPCO) and royalty-based pharmaceutical company (RIPCO)—to fully integrated discovery and development organization (FIDDO) model, which means genotech companies focusing on drug development and delegating manufacturing, sales, distribution, and marketing. BIOTECH 95, *supra* note 2, at 40; Kathleen Day, *Experimental Journey*, WASH. POST, Mar. 27, 1995, at 1, 18-19 ("Most companies don't have the illusion anymore that they'll become fully integrated, stand-alone pharmaceutical companies that can do everything. . . . Money is scarce out there."). Lawrence M. Fisher, *With New Genentech Chief, Science Takes Center Stage*, N.Y.TIMES, July 12, 1995, at D2 (stating that the ousting of G. Kirk Raab and naming of Arthur D. Levinson as president and chief executive "is a clear signal that first and foremost Roche [Holding Ltd.] intends Genentech to be a research and development center, with sales and marketing largely handled by the parent company."). The FIDDO model is built upon an alliance philosophy, in which the biotech company "could partner with academia for discovery; partner with CROs for clinical and preclinical development; partner with pharma companies for marketing, distribution, and sales; and even partner with others for manufacturing." BIOTECH 95, *supra* note 2, at 40. Making genotech companies members of alliances around a shared technology and objective (developing and marketing that technology) cuts risks to genotech investors and enhances genotech company's attractiveness to investors, though it also restricts their potential for profit. *See* James Flanigan, *What Ails the Drug Industry Has Little to Do With Politics*, L.A.TIMES, May 25, 1994, at D1.("Drug stocks are declining because market forces are driving the air out of drug prices, forcing the pharmaceutical industry into a historic restructuring. Powerful trends in the business show that drug companies will continue to merge and consolidate and important drug

There has thus been a rapid shift in involvement and contributions from the government to the private sector. The private sector is now assuming the economic risks and costs of developing practical applications of genotechnology. Nevertheless, the accomplishments of the industry rest upon a regulatory infrastructure supportive of R&D and the direct contributions of the federal government, as discussed below in Section II. The end result is an industry built upon a conglomeration of complex alliances between the private and public sectors—alliances among members of industry, academia, and government arranged in a staggering number of ways.[91]

This entanglement between the public and private sectors has been a source of controversy as rights allocation issues at least as complex as the underlying alliances are already arising.[92] These are the latest in a series of ethical and legal issues which have emerged over the course of the industry's development. Despite the industry's growing significance, many of these issues remain largely unaddressed.[93]

1. *The Exodus From Government and Academia to the Genotechnology Industry*

From its inception, the genotech industry has been tied closely to academia, a traditional source of pure scientific research heavily funded by the federal government.[94] What distinguishes genotech from analogous fields is the willingness of academics either to enter into joint development agreements with genotech firms, or to leave their academic and government posts altogether to join existing genotech companies or start their own. Academic institutions and teaching hospitals—unwilling to give up affiliations with these leaders in the field of genotechnology and miss out on the prestige and potential financial gain associated with the genotech industry—also are getting directly involved in the research, development and commercialization of

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research will increasingly be done by smaller biotechnology companies."). Some in the genotech industry, such as ImmuLogic, redefined their objectives before the down-turn in investment. *See Hits and Misses for Biotech Class of '91*, BOSTON GLOBE, Oct. 2, 1994, at 84 ("[T]he ImmuLogic strategy was different from some other biotech companies, which eschewed alliances with major pharmaceutical companies, hoping instead to become fully integrated companies with their own research, manufacturing and sales forces." Founder and chairman, Malcolm Gefter, says, "I watched Genentech, which had huge fixed costs for commercializing their products and then had to wait for [Food and Drug Administration] approval and recognized the potential pitfalls in the developing process . . . ."). Leaders in the genotech industry, however, are buying up their successors. *See* BIOTECH 96, *supra* note 2, at 7 (Amgen buying Synergen).

91. For a good summary of how consortiums may be pieced together, see BIOTECH 96, *supra* note 2, at 34.

92. *See, e.g., infra* note 341-345 and accompanying text (addressing BRCA1 controversy).

93. These ethical issues are identified and addressed briefly *infra* Section III.D.

94. *See infra* Section II.C (addressing NIH funding of basic research).

genotech-based advances.

The exodus of genotech researchers from government and academia to private industry predates the modern genotech industry. In 1973, Herbert Boyer and Stanley Cohen were the first to clone genes, accomplishing this while working at Stanford University.[95] Shortly thereafter, Boyer left and, with venture capital provided by Robert Swanson, founded Genentech.[96] This pattern—university researchers moving into the private sector or forming alliances with genotech firms—was repeated and, with each repetition, the web of connections among government, academia and industry became increasingly entangled.[97]

The trend undoubtedly has been furthered by the federal government's fostering of a genotech industry through HGP and its technology transfer policy.[98] For example, Dr. Craig Venter, working on the government-funded HGP at NIH, invented a method for identifying gene sequences, thereby igniting the patent controversy discussed below.[99] With this method and $70 million from venture capitalists in hand, Venter left the NIH in 1992 and founded a not-for-profit research institution, The Institute for Genomic Research (TIGR), and a for-profit counterpart, Human Genome Sciences, Inc. (HGS), to commercialize TIGR's findings.[100] TIGR and HGS have been busy carrying on the work identifying gene sequences which Venter began at the NIH, filing thousands of patent applications to protect their findings, and developing ways to commercialize them.[101] They have compiled an extensive database of identified gene sequences and, in September 1995, opened certain parts of this database to academic and government researchers who previously had been allowed accesss only if they were willing to give HGS licensing

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95. Carey, *supra* note 8, at 77.

96. Joan O'C. Hamilton, *Biotech's First Superstar—Genentech is Becoming a Major-Leaguer—and Wall Street Loves It*, BUS. WK., Apr. 14, 1986, at 68.

97. *Cf.* Johnson, *supra* note 27, at 6 ("The search for capital has spurred extraordinary creativity among biotech companies and their investors in structuring alternative financing techniques . . . .").

98. *See infra* Sections II.A, II.B.1.

99. Carey, *supra* note 8, at 74; *see also infra* notes 198-203 and accompanying text.

100. Carey, *supra* note 8, at 76.

101. *Id.* at 74, 77. The controversy surrounding Venter's career has been summarized as follows:

> Depending on one's perspective, Venter and his company typify the ideal link between government-supported basic science and the entrepreneurial verve necessary for seeing that the fruits of [the] Human Genome Project make their way into the medical marketplace. But some scientists are uneasy—ethically and professionally—with the idea of their colleagues profiting from the research for which the government has paid . . . . All the work [Venter] produced at the National Institutes of Health was published in scientific journals that were available to the public, [Venter] . . . said, and he has had little to do with the financing he has received since leaving the government.

Fisher, *supra* note 31, at 9A. *See generally* Carey, *supra* note 8.

rights to their discoveries.[102]

Revolving doors among academia, government and industry are now characteristic of the genotech industry.[103] Examples are plentiful. Millennium Pharmaceuticals, co-founded by an MIT professor, employs former academics[104] and lists the director of the federally funded Whitehead/MIT Center for Genomic Research and professors at Rockefeller University and Albert Einstein College of Medicine among its founding scientific advisors.[105] Chiron Corp., one of the few remaining integrated genotech firms,[106] was founded by three scientists from the University of California at Berkeley.[107] Myriad Genetics was co-founded by Walter Gilbert, a Harvard University academic, and Darwin Molecular was co-founded by Dr. Leroy Hood of the University of Washington.[108] Richard Myers and Dennis Drayna, affiliated with the federally funded Genome Center in Palo Alto, California, formed Mercator Genetics.[109] Mark Pearson, a member of the federally funded HGP's national advisory board, is CEO of Darwin Molecular.[110] Dr. Ronald G. Crystal, once extensively involved in *in vivo* gene therapy as a chief scientist at the NIH, is now a founder of and Chief Scientific Advisor at GenVec.[111]

This exodus to the private sector and rush to commercialize emerging science has generated resentment within the genotech field:

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102. Elyse Tanouye, *Biotechnology: Gene Pioneer Opens His Databank . . .*, WALL ST. J., Sept. 28, 1995, at B1, B16; *see also supra* note 63 (discussing use of database by Johns Hopkins researchers to identify gene associated with colon cancer); *infra* note 336 (discussing HGS's practice of licensing its database and Merck's efforts to make similar information freely accessible).

103. The revolving door also exists within the genotech industry itself as executives move between companies. *See, e.g.*, Don Clark, *Raab Is Named Chairman of Shaman, Two Months After Genentech Ouster*, WALL ST. J., Sept. 14, 1995, at B10 (Former Genentech CEO who resigned after Board probe revealed his secret request for $1 million personal loan guarantee from Roche Holding, Genentech's majority stockholder, resurfaced as chairman of Shaman Pharmaceuticals, a small biotech firm developing drugs from tropical plants.).

104. Thomas M. Burton, *Eli Lilly Plans Gene-Research Venture With Millennium in Bid for New Drugs*, WALL ST.J., Oct.24, 1995, at B6 (Millennium co-founded by Eric Lander, professor at MIT's genome center).

105. Ronald Rosenberg, *Biotech Thrives on the Hot Idea*, BOSTON GLOBE, Apr. 10, 1994, at A77.

106. *See infra* Section III.A (few remaining genotech firms are capable of moving drugs from R&D to market without assistance from pharma partner(s)).

107. *Chiron Stock Jumps Amid Merger Talk Rumors: Biotech Firm Confirms It's Discussing Alliance with a Company*, SAN JOSE MERCURY NEWS, Nov. 12, 1994, at 12D.

108. Bylinsky, *supra* note 8, at 95.

109. Fisher, *supra* note 101, at 9A.

110. *Id.*

111. *GenVec Acquires Promising New Gene Therapy Cancer Technology: Exclusive Patents Offer Promise for Precise Therapy at Tumor Sites*, GENVEC PRESS RELEASE (GenVec Corporation), Nov. 29, 1993.

> The commercial recruitment of leading scientists from publicly supported universities and federally backed genome centers has stirred professional resentment among some geneticists, who argue that the rush to commercialize or patent pieces of the genome project will hinder the greater discoveries that can come when the scientific community freely shares its discoveries.[112]

This resentment has been displayed in allegations of conflicts of interest and professional impropriety. For example, the PTO has a number of examiners who formerly worked at the NIH. Those examiners are reviewing patent applications from firms with executives and employees who are also former NIH employees. This has resulted in allegations of PTO favoritism.[113] Such allegations are likely to increase as more technologies reach commerce and individuals begin to realize substantial profits from genotechnologies that originated through government research and funding.

Despite this controversy, the trend shows no signs of stopping, or even slowing. In fact, final FDA-approval of technologies, recent scientific successes with immensely lucrative commercial potential,[114] the return of market appeal to investors and pharma investment, and the impact of potential congressional budget-cutting on publicly-funded research and development are likely to cause the exodus to continue and expand.

2. *The Prevalence of Alliances*

As discussed below, progressing from genetic discovery to marketable drug is a capital-intensive project, often costing as much as $300-400 million and taking ten to twelve years.[115] The federal government, through the HGP, NIH, and Federal Technology Transfer policy, has been involved in much of the basic genotech research.[116] Accordingly, alliances between private genotech companies and the government, in the form of cooperative research and development agreements (CRADAs),[117] are long-standing. Also, direct involvement from the researchers and scientists whose work has formed the basis of the industry is, as a practical matter, often needed by companies seeking to build commercial entities around such work. These researchers are commonly affiliated with academic institutions, making alliances between

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112. Fisher, *supra* note 101, at 9A.

113. *See infra* note 428.

114. E.g., Amgen's discovery of leptin, a hormone found to significantly control obesity in mice. *See supra* note 51 and accompanying text.

115. *See infra* Table I accompanying note 251. *See generally infra* Sections II.D and III.A.

116. *See infra* Section II.

117. *See infra* Section II.B.1 for discussion of CRADAs.

genotech companies and academia a natural and necessary development.[118] Depending upon the outcome of present and future budget cuts, the most prestigious academic institutions and teaching hospitals, which have benefitted from federal government largesse and were once too uncomfortable with these alliances to engage in them, may pursue genotech companies aggressively on behalf of their faculty, staff and patients.[119] The commercial success of genotech may have the same effect. In fact, beyond shifting some of the cost of their faculty's research to genotech companies and investors in those companies, royalties from the forthcoming genotech therapeutics and diagnostics may be a means for such institutions to offset expected cuts in government subsidies.

Outright alliances between academia and industry are pervasive and recently have taken on a more commercial flavor than is customary for academics. For example, Harvard University and Genica are working together on a potential eye test for Alzheimer's disease. Pursuant to their agreement, Genica receives exclusive rights to market the test while Harvard receives royalties on future sales.[120] In 1994, HGS announced a collaboration with Johns Hopkins University School of Medicine to research genes identified by TIGR and HGS that may play a role in colon cancer.[121] Johns Hopkins granted HGS an exclusive license to the results of the project in return for access to HGS's gene sequence database.[122] HGS also has over thirty agreements with nineteen different research institutions, most of which are university affiliated.[123] To compete with HGS in the identification of gene sequences, Merck & Co. paid Washington University to sequence 200,000 gene fragments.[124] Additionally, Amgen is paying MIT $3 million per year

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118. Note also that, since academia has traditionally received research funding from the federal government, alliances with academia have allowed firms to leverage that government funding—an indirect means for firms to obtain government subsidization as opposed to the direct funding received by firms under CRADAs.

119. *See* Travis E. Polling, *Financing the Studies: Faced with Stagnant Federal Funding, Institutions Seek More Private Contracts*, SAN ANTONIO BUS. J., July 21, 1995, at 15 ("The focus of academia tends to be squarely on federal sources when it comes to funding, but locally and nationally academic research institutions are having to look beyond Washington, D.C., to keep their projects funded and researchers busy."); *supra* note 112 and accompanying text.

120. Dolores King, *Harvard, Biotech Firm Strike Deal*, BOSTON GLOBE, Nov. 11, 1994, at 1.

121. HUMAN GENOME SCIENCES, INC., HUMAN GENOME SCIENCES TO COLLABORATE WITH JOHNS HOPKINS MEDICAL SCHOOL ON COLON CANCER RESEARCH (Feb. 28, 1994).

122. *Id.; see also supra* note 63 (describing Johns Hopkins' efforts to identify cancer gene).

123. HUMAN GENOME SCIENCES, INC., HUMAN GENOME SCIENCES ANNOUNCES NEW AGREEMENTS WITH RESEARCH INSTITUTIONS 1 (July 21, 1994).

124. Carey, *supra* note 8, at 76; *cf.* Robert Rosenberg, *Genzyme's Plans to Beat Obsolescence*, BOSTON GLOBE, Jan. 8, 1995, at 57 (Genzyme working with University of Pittsburgh researchers and Dutch genotech firm to develop gene therapy technique).

for ten years for rights to some of the school's biological research.[125]

Many of these academia-industry collaborations have taken on the appearance of commercial joint ventures. For example, Genetics Institute, Inc. (GI) and Johns Hopkins University School of Medicine combined to form MetaMorphix, Inc., a company focusing on treatments to repair the nervous system.[126] GI invested $3.6 million for a fifty-eight percent share of the company, while Johns Hopkins contributed nineteen genes for the remaining forty-two percent.[127] Johns Hopkins will receive royalties based upon its contribution to a particular product when that product is sold either by GI or MetaMorphix.[128] GI has the right to commercialize any discoveries by MetaMorphix which MetaMorphix decides not to develop and market itself.[129] As observed by one commentator, "[t]raditionally[,] what happens with academic centers that have licensing agreements with companies is that scientists get small royalties. . . . In this situation, though, it seems that the scientists get more control. It is an expanded collaboration that goes one step beyond the traditional agreement."[130]

Johns Hopkins also has filed jointly with Integrated Genetics, a division of Genzyme Corp., for a patent to commercialize decoded genetic information involved in kidney disease.[131] This alliance was reported in the popular press as:

> an example of a trend in biotechnology research, in which university scientists team with small biotech companies. Such relationships offer long-term financial incentives to universities, which stand to make money if products result from the efforts, and immediate gain to struggling start-up companies, which are often strapped for cash and need additional brainpower.[132]

However, the alliance between Johns Hopkins and Integrated Genetics also provides an example of the potential for controversies such as arguments over intellectual property rights and questions of divided loyalties, which often surround many such agreements. Johns Hopkins and Integrated Genetics relied

125. Ronald Rosenberg, *Amgen to Get Synergen for $240 Million*, BOSTON GLOBE, Nov. 19, 1994, at 25.

126. Cathryn J. Prince, *Genetics Institute, University Form Baltimore Research Firm*, BOSTON BUS. J., May 26-June 1, 1995, at 11.

127. *Id.*

128. *Id.*

129. *Id.*

130. *Id.*

131. *Mass. Firm, Johns Hopkins Announce Kidney Disease Find*, BOSTON GLOBE, Apr. 2, 1995, at 13.

132. *Id.*

on assistance from a scientist at Los Alamos National Laboratory to help them understand how the gene's proteins cause adult polycystic kidney disease, yet there is no mention of the government scientist's being named on the patent.[133] The BRCA1 dispute, discussed in Section III.B, also dramatizes the problem of allocating rights when government, academia and industry combine to form a product with commercial value.[134]

Additionally, the ethical implications of these collaborations have not been explored. Some scientists have expressed concerns that the expectations of investors financing genome companies have created and will continue to create pressures that scientists are hard-pressed to resist—perhaps resulting in overly-optimistic reports on research, if not outright scientific fraud.[135] Moreover, this investor pressure to generate profits may have skewed the course of basic science in the genotechnology field, thereby contributing to a "false start" for the industry. Some commentators fear that financial pressures are replacing "scientific rigor in determining how and when to use gene therapy" and sacrificing basic scientific research and human safety for a quick profit as "[c]ommercial pressure has . . . pushed scientists to test gene treatments on human subjects as early as possible."[136]

Nevertheless, existing alliances are only the beginning. As the genotech industry continues to consolidate,[137] genotech firms are investing in other genotech firms.[138] The most significant example is the Amgen takeover of

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133. *Id.*

134. *See, e.g.*, King, *supra* note 120, at 1 (reporting that Genica Pharmaceuticals Corporation began marketing a test for a gene that may indicate the risk of Alzheimer's disease, even though it had no agreement with Duke University, which conducted the original research); *infra* text accompanying note 341.

135. Fisher, *supra* note 101, at 9A (noting that roles must be clearly defined to avoid inherent conflict of interest).

136. Gorman, *supra* note 16.

137. Rosenberg, *More Woes*, *supra* note 87, at 61 (noting that 1994 was a bad year for biotech with only one drug receiving FDA approval, and that, "[i]n the year ahead, analysts are expecting tougher times for weaker biotech firms, including more fire sales of assets and technology sales to stronger biotech firms and to large pharmaceutical firms"); Steve Kaufman, *Bio-Roulette Failures Have Cut the Flow of Funds to Biotech, But Big Rewards Tempt Some Investors*, SAN JOSE MERCURY NEWS, Nov. 28, 1994, at 1D ("A big shakeout is imminent among the industry's 1,311 companies, and it will probably hit venture capital-backed players hardest because they are the furthest from introducing products. The best guess among many industry insiders is that about half of all companies will be gone within about five years."). Although this trend has not been as extensive thus far as was anticipated, it is expected to continue. *See* BIOTECH 96, *supra* note 2, at 5 (statement of Dr. Arthur D. Levinson, President and CEO of Genentech, Inc.). As this Article goes to print, the market appeal of genotechnology has largely returned. *See supra* note 32.

138. Johnson, *supra* note 27, at 6 ("Corporate investments have . . . become popular as a way for profitable public biotech companies interested in preserving earnings to fund new technical opportunities on an 'off balance sheet' basis while retaining marketing rights to the developed products."); *see also* Clark, *supra* note 103 (Raab planning to assemble fund to buy small biotech firms and consolidate them into a larger company).

Synergen for $240 million in 1994.[139] Genentech invested $17 million in GenVec[140] which, in turn, later merged with Theragen.[141] Other companies, including HGS, have a portfolio of deals with other genotech firms.[142]

In their efforts to form alliances, genotech companies' attentions have shifted to pharmas.[143] Especially during times of low market appeal to investors, this match seems ideal, enabling genotech firms to leverage existing pharma expertise in manufacturing, marketing, and dealing with the FDA and other regulatory bodies, both domestic and foreign.[144] Multinational pharmas are better positioned than small genotech firms to be aware of and exploit comparative market advantages such as clinical trials conducted abroad. Additionally, pharmas, with their portfolio of products, are more capable of absorbing losses when particular products fail, thereby perhaps stabilizing the market for genotech companies' stocks.[145] Finally, pharmas are in need of new products as patent expiration dates on many of their major drug products are approaching.[146]

Pharmas are investing in the genotech industry in a myriad of ways.[147]

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139. Sutherland, *supra* note 87, at D1. According to a Paine Webber analyst, this takeover may have marked the "beginning of the end for the biotech industry as an assortment of small, speculative independent companies trying to play David to the drug industry's Goliath . . . ." *Id.*

140. *See* GENVEC CORP., GENVEC ACQUIRES PROMISING NEW GENE THERAPY CANCER TECHNOLOGY 1 (Nov. 29, 1993).

141. GENVEC CORP., TWO GENE THERAPY COMPANIES FINALIZE MERGER (Sept. 6, 1994).

142. *See, e.g.*, HUMAN GENOME SCIENCES, INC., HGS AND GENETIC THERAPY FORGE GENE THERAPY COLLABORATION (Sept. 14, 1994); HUMAN GENOME SCIENCES, INC., HGS AND GENENTECH TO COLLABORATE (Apr. 20, 1994).

143. *See generally*, BIOTECH 96, *supra* note 2, at 49-50 (describing 10 most influential deals in the industry). Ronald Rosenberg, *From Foes to Financiers*; BOSTON GLOBE, Nov. 24, 1995 at 89, 92.

144. *See e.g.*, Rosenberg, *supra* note 143.

145. *Id.*

146. Johnson, *supra* note 27, at 4 (Nov. 18, 1993) ("Many large pharmaceutical companies have recognized that they need to increase their rate of development of new products and that biotechnology is the most promising method to do so. Companies with major products which are soon coming off patent (such as Glaxo with Zantac, SmithKline with Tagament and Syntex with Naprosyn) are particularly vulnerable and motivated. Their willingness to enter into creative collaborative relationships with younger biotech companies has taken a substantial part of the load off venture investors in financing young biotech companies from inception to profitability.").

147. *See generally* BIOTECH 96, *supra* note 2, at 49-50 (listing 10 most influential deals). SmithKline Beecham invested $125 million in HGS for a 7% equity position and rights to promising genes. Carey, *supra* note 8, at 73. Rhône-Poulenc Rorer, Inc. has invested $5 million for an equity position in Darwin Molecular. DARWIN MOLECULAR, CORP., DARWIN SIGNS AGREEMENT WITH RHÔNE-POULENC RORER; COMPLETES FINANCING ROUND (Oct. 4, 1994). Hoffman-LaRoche owns 60-percent of Genentech and has invested $70 million in Millennium Pharmaceuticals. *Survey, supra* note 2, at S6; Rosenberg, *supra* note 105. Eli Lilly paid almost $3 million to Myriad Genetics for rights to the BRCA1 gene. Bylinsky, *supra* note 8, at 95. Other pharmas are paying genotech firms just for the opportunity to look into their databases. Carey, *supra* note 8, at 76; *see also* Burton, *supra* note 104 (Eli Lilly and Millennium Pharmaceuticals

The fully-integrated entrepreneurial genotech companies that could both discover and produce genotech products are becoming R&D centers dependent upon pharmas for drug approval, manufacturing, and international and domestic marketing.[148] In fact, of the nation's dozen or so major biotech companies, only Amgen has been able to remain independent—and rumors persist that Amgen is up for sale.[149]

It is too soon to tell whether these alliances will bode well for the industry.[150] With the return of investment appeal, the genotech industry may be less dependent upon pharmas, except to the extent that the return of this

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entering into $50 million joint venture); Lawrence Fisher, *Therapy with Genes Gains in Credibility*, ORANGE CTY. REG., June 4, 1995, at D6 (big drug firms such as Bayer, Rhône-Poulenc Rorer and Sandoz are investing big money in joint development deals with new companies, including Applied Immune Sciences, Somatix Therapy, and Systemix); Gorman, *supra* note 16, at 63 ("The list of recent mergers . . . reads like a Who's Who of biotechnology: 'Sandoz buys Genetics Institute. Chiron buys Viagene. Bristol Myers makes a big investment in Somatrix . . . Rhône-Poulenc invests in Applied Immune Sciences and several other gene-therapy companies.'"); Robert Langreth, *New Technique for Discovering Medicines Takes Hold*, WALL ST. J., Sept. 11, 1995, at B3 (discussing combinatorial chemistry, a new drug discovery technique that allows chemists to speed up development of new substances and is driving pharmas' "new round of gobbling up small biotechnology companies," citing Glaxo Wellcome's acquisition of Affymax NV, Marion Merrell Dow's purchase of Selectide, Inc., and Eli Lilly's purchase of Sphinx Pharmaceuticals as examples). *But see Repligen Says Lilly Is Out Of Drug-Development Pact*, WALL ST. J., Sept. 13, 1995, at B9 (Eli Lilly backing out of agreement to fund Repligen's development of monoclonal antibodies for inflammatory diseases, after string of setbacks for Repligen); Thomas M. Burton and Rhonda L. Rundle, *Lilly Gets Out of Biotechnology and Medical Diagnostics*, WALL ST. J., Oct. 2, 1995, at B4 (Eli Lilly selling off biotech assets to Beckman Instruments, Inc. at fraction of price it originally paid).

148. Rosenberg, *More Woes*, *supra* note 87, at 61; *cf.* Day, *supra* note 90, at 18 (blaming investors' flight from the industry for driving some biotech companies out of business and forcing others to acquiesce to giant pharmaceutical take-overs); Ronald Rosenberg, *Repligen Cuts Nearly Half its Staff*, BOSTON GLOBE, Feb. 15, 1995, at 41-42 (company cut work force by nearly 50% and postponed or discontinued promising drug development in desperate attempt to conserve cash). Genotech companies working on the same technologies are merging to eliminate duplication and rechannel resources to diversify—"like two people sharing two lottery tickets rather than each holding one with perhaps the same numbers." Day, *supra* note 90, at 1, 18-19 (citing the sale of Crop Genetics International Corp. of Columbia to Biosys Inc. of Palo Alto, California and a merger between Oncologix Inc. of Gaithersburg and two Texas firms, Argus Pharmaceuticals Inc. and Triplex Pharmaceutical Corp.). *See supra* note 90; (addressing FIPCO, RIPCO, and FIDDO organizational models).

149. However, Amgen also has a number of deals with pharmas. *See* BIOTECH 96, *supra* note 2, at 49-50 (Amgen partnering with drug firms such as J & J and Roche); *cf.* Kathleen Day, *Biotech Company Fills Prescription for Success*, WASH. POST, Aug. 21, 1995, at 9 ("As health care insurers and providers push to contain rising medicinal costs even large drug companies have found it hard to remain independent."). Most of the biotech companies' deals have been large and narrowly targeted around specific technologies, such as SmithKline Beecham's $125 million deal with HGS and Hoffman LaRoche's $70 million deal with Millennium. *See* Lawrence Fisher, *Rhône Unit Focuses on Gene Drugs*, N.Y. TIMES, Nov. 15, 1994, at D5 (discussing how Rhône-Poulenc Rorer has created a new division concentrating on R&D and commercialization of drugs based on gene and cell therapies).

150. *See* Gorman, *supra* note 16, at 63 (noting that pharma investment, while probably unavoidable, may prematurely push science out of basic research and into a rush to market).

appeal is attributable to pharma involvement. The genotech industry's alliances are a direct result of supportive federal policy. Now, policymaking regarding the commercialization of genotechnology must be as direct, responsive, and comprehensive as the federal policy promoting genotech R&D. Section II sets forth an overview of federal policy generally, while Section III assesses that policy and makes proposals for change.

II. Federal Financial Support and the Regulation of Genotechnology

Just as the United States engaged in the Manhattan Project to develop the atomic bomb and end World War II, the Apollo Project to beat the Soviets to the moon, and the Cold War to deter the use of nuclear weapons, the United States has made a deliberate and substantial effort to advance genotech R&D. Smith and Kettelberger claim, "Not since the dawn of the atomic age have scientists from all over the world sought the same prize."[151] Although the primary objective of federal policy presumably has been to improve human health, there have been economic returns on the federal government's support—as evident from the fact that the genotech industry exists almost entirely within the United States' borders.[152]

HGP is the United States' most direct and perhaps most publicized statement of support for advancement within the field of genotechnology. In fact, the federal government—through the NIH, FDA, and PTO—has had an impact on the past and current state of the genotech industry and will also shape the industry's future. The following is a discussion of how the United States, through these agencies and relevant statutes and regulations, has supported the industry.

A. *The Human Genome Project*

HGP is an effort, initiated by Congress in 1988-89 and commenced in 1990, to map all twenty-three pairs of human chromosomes. The three primary technical goals of the project are to produce (1) genetic linkage maps to trace inheritance of chromosome regions through pedigrees; (2) physical maps of large chromosome regions to enable direct study of DNA structure in search of genes; and (3) substantial DNA sequence information, enabling the correlation of DNA changes with alterations in biological function.[153] Some

151. G. Kenneth Smith & Denise M. Kettelberger, *Patents and the Human Genome Project*, 22 A.I.P.L.A. Q.J. 27, 39 (1994) (addressing support of various governments for protecting and fostering genotech).

152. *See supra* note 2.

153. Robert M. Cook-Deegan, *Origins of the Human Genome Project*, 5 RISK: HEALTH, SAFETY & ENVIRONMENT 97, 100 (1994). The fact that the overall objective of HGP is to map the human genome has generated extensive criticism within the scientific community. "Some

350 laboratories throughout the world now are engaged in HGP.[154] Despite the elimination of federal programs to fulfill the Republican Congress' "Contract with America," the Project is targeted to receive more than $100 million in federal funds per year through its completion in 2005, unless it is completed sooner.[155]

HGP intentionally seeks to join the commercial and academic sectors to exploit the rapidly growing body of knowledge about DNA structure in order to generate practical benefits for human health. As discussed above, the result has been alliances among academic, not-for-profit, and private individuals and entities around specific technologies. Public funds designated for academic research and private funds have been commingled—feeding the impression that public money is being used for private gain.[156] Critics charge that academic-industrial alliances will slow or halt the transfer of gene mapping and sequencing research, adding needless time and money to complete the genome sequencing.[157] These are just some of the serious policy and economic isues associated with the HGP.[158] Nevertheless, HGP clearly satisfies a cost-benefit analysis based on the real dollar investment associated with it. Public funds reaching private industry through HGP are trivial in comparison with the investment of private industry—$1.5 to $2 billion in 1987, some three years *before* HGP even commenced.[159] The practical effect of HGP cannot be overestimated. HGP is responsible for generating world-wide scientific, political, and financial commitment to the field of genotechnology. It has spurred scientific advances in the field in record time and thereby created a multiplication effect on private-sector investment, first from venture capitalists and now from pharmas.[160]

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critics assess that it would be preferable to spend the limited funds available to determine the complete structure and function of individual genes of medical importance." Kirby, *supra* note 33, at 8.

154. Bylinsky, *supra* note 8, at 100.

155. Although the monies appropriated to HGP are reviewed annually and subject to cuts, this sum has increased over the past several years from $106 million in 1993, to $108 million in 1994, to $114 million in 1995. Telephone Interview with Sharon Durham, Public Affairs Specialist, Nat'l Ctr. for Hum. Genome Research (Aug. 1, 1995). Current federal budget-cutting efforts are expected to result in a reduction of only $1 million for 1996. *Id.*; *see also* Victor A. McKusick, *The Human Genome Project: Plans, Status, and Applications in Biology and Medicine*, *in* GENE MAPPING: USING LAW AND ETHICS AS GUIDES 18, 22-26 (George J. Annas & Sherman Elias eds., 1992); James D. Watson, *The Human Genome Project: Past, Present, and Future*, 248 SCIENCE 44, 46-47 (1990). For an example of how federal grants from DOE and NIH are funding the research of Genome Therapeutics, Inc. of Waltham, Massachusetts, *see* Ronald Rosenberg, *Taking Gene Therapy to the Market*, BOSTON GLOBE, Jan. 22, 1995, at 80.

156. *See supra* Section I.B; Smith & Kettelberger, *supra* note 151, at 50.

157. Smith & Kettelberger, *supra* note 151, at 50.

158. *See infra* Section III.

159. Rebecca S. Eisenberg, *Patenting the Human Genome*, 39 EMORY L.J. 721, 737-38 (1990).

160. *See generally supra* note 99 and accompanying text.

HGP has inspired the European Union and some individual countries to finance parallel efforts.[161] For example, the United Kingdom committed £15 million from 1989 to 1992. Several other European countries likewise have devoted specific government funds to the project, and Canada has allocated $18 million over the next five years.[162] These government funds have been supplemented by money from charities, such as the Howard Hughes Foundation in the United States and the Welcome Trust in the United Kingdom. In addition, the Human Genome Mapping Project administered by the Medical Research Council in the United Kingdom, the Science and Technology Agency of Japan, and the combination of the French Muscular Dystrophy Association, Genethon and le Centre d'Etude du Polymorphisme Humain of France have made direct contributions to the field.[163] HGP also has inspired the creation of the Human Genome Diversity Project (HGDP), a collaborative effort among anthropologists, geneticists, doctors, linguists, and scholars throughout the world to document genetic variation within the human species.[164]

World-wide efforts in the field of genotechnology are coordinated, albeit loosely at times, through two international organizations—HUGO and the United Nations Educational, Social, and Cultural Organization (UNESCO). HUGO, established in 1989 in Geneva, Switzerland, is comprised of an international group of scientists and operates by coordination among people—rather than nations—in the Project. It claims to be an "enabler" instead of a "provider" or rule creator.[165] Although HUGO has no formal

161. *Survey, supra* note 2, at S9. The efforts of other nations are discussed country-by-country in Smith & Kettelberger, *supra* note 151, at 50. In order to encourage industry expansion, the Senior Advisory Group on Biotechnology (SAGB), which is composed of Europe's biotech company leaders, has petitioned the European Union for a change in its regulatory policies. BIOTECH 95, *supra* note 2, at 15. SAGB has also recommended the creation of a task force with a defined mission to confront current obstacles to biotechnology industry growth. The plan would include, *inter alia*, revision of regulatory guidelines; changes in investment policies so as foster entrepeneuralism; and greater education funding. *Id. But see infra* note 213 (describing European Parliament's action in vetoing legislation to clarify conditions under which genes may be patented in EU).

162. Kirby, *supra* note 33, at 9.

163. Smith & Kettelberger, *supra* note 151, at 32-33.

164. Since January 1994, HGDP has been carried out under the auspices of the Human Genome Organization (HUGO). UNESCO is, at the outset of HGDP, taking care to address ethical implications of the collection of DNA samples. *See generally*, Bartha Maria Knoppers et al., *Ethical Issues in International Collaborative Research on the Human Genome: The HGP and the HGDP* (unpublished manuscript, on file with authors). According to Professor Knoppers and her colleagues, who are highly regarded for their international perspective, a "macro-ethical" framework focusing on *both* communities and individuals must be established for *both* HGDP and HGP. *Id.* at 4. Like HGP, HGDP has generated criticism, including a 1993 commmuniqué from Rural Advancement Foundation International (RAFI) and a 1993 Declaration on Cultural and Intellectual Property Rights of Indigenous Peoples by MATAATUA. *Id.* at 6.

165. Kirby, *supra* note 33, at 9-10.

decision-making powers, its recommendations carry "moral weight."[166] UNESCO, located in Paris, France, has not been as active as HUGO, but it has succeeded in encouraging regional and national discussions of the ethical and legal issues associated with research and advancements in the field of genotechnology.[167]

B. *Property Rights and Other Market Protections*

The federal government has encouraged investment in genotechnology both by directly funding research and by granting property rights and other market protections to research results. The government is (1) giving government-funded R&D to the private sector; (2) granting patent protection to the private sector's genotech advances; and (3) protecting specific markets for genotech products.

1. *Federal Transfer of Technology Policy*

The United States is making scientific contributions and giving them—along with the tremendous financial risks accompanying their development—to the private sector. The underlying hope is that the private sector will commercialize these contributions and, consequently, benefit public health. The exercise of existing statutory authority to transfer technology as well as provisions in proposed legislation directly tailored to the business of genotechnology demonstrate the federal commitment to the industry.[168]

Under the Stevenson-Wydler Technology Innovation Act[169] and the Bayh-Dole Act,[170] the United States has given small businesses and nonprofit organizations a statutory right to retain title to technology and innovations realized through federally-assisted R&D, so long as they are interested in patenting and attempting to commercialize this technology.[171] The Bayh-Dole Act was expanded in 1984 to apply to not-for-profit government-owned, contractor-operated facilities (GOCOs).[172] Under the Federal Technology Transfer Act (FTTA), enacted in 1986, those employed by agencies may patent

166. *Id.*

167. *Id.* at 10.

168. Note that, unless otherwise indicated, federal technology transfer law applies to the transfer of *all* technology, not just that associated with genotech.

169. Pub. L. No. 96-480, 94 Stat. 2311 (1980) (codified at 15 U.S.C. §§ 3701 (1980)) (technology innovation/transfer).

170. Pub. L. No. 96-517, 94 Stat. 3020 (1980) (codified at 35 U.S.C. §§ 202 (1980)); *see also* 35 U.S.C. § 203 (1980) (patent rights in inventions made with federal assistance).

171. *See generally* Lawrence Rudolph, *Overview of Federal Technology Transfer*, 5 RISK: HEALTH SAFETY & ENV'T 133, 134 (1994).

172. *Id.*

inventions if their agency employer does not intend to do so. The FTTA also (1) authorizes cooperative R&D agreements between federal laboratories and nonfederal entities; (2) requires royalty sharing with federal employees whenever an agency retains ownership of its inventions; and (3) authorizes award programs for such employees. The American Technology Preeminence Act of 1991[173] extended the Stevenson-Wydler Act to agencies within the legislative branch.

On a practical level, the FTTA has created incentives for high tech companies to join with the NIH and other government agencies to work together on the research and development of new technologies. These incentives encourage the creation of biotech firms concentrating on the development of new pharmaceuticals.[174] For example, Human Genome Sciences, Inc. (HGS), a company formed largely to identify genetic sequences and find commercial applications for them, uses a technique developed at the NIH to catalogue the chemical sequence of human genes.[175] Likewise, the Bayh-Dole Act has permitted universities to retain title to their federally funded inventions and to grant licenses for patents arising from inventions.[176]

These policies benefit the genotech industry most obviously through the prevalence of cooperative research and development agreements (CRADAs)—contractual agreements that create actual privity between federal laboratories and private entities for the development of specific technologies.[177] Executive Order 12591, issued in 1987, directed federal agencies to encourage cooperative research and technology transfers through their laboratories.[178] In 1989, the National Competitiveness Technology Transfer Act authorized Department of Energy (DOE) laboratories to enter into CRADAs on the same basis as GOCOs. To foster such agreements, the Act created a Freedom of Information Act exemption for certain categories of

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173. Pub. L. No. 102-245, 106 Stat. 7 (1992) (also known as the Technology Administration Act).

174. Day, *supra* note 90, at 19.

175. *Id.*; *see also supra* note 102 and *infra* notes 336 and 382 (discussing HGS and its sequencing efforts in more detail).

176. *See also* David Warsh, *Lab-to-Market Miracle at MIT*, BOSTON GLOBE, Oct. 31, 1995, at 41 (reporting that universities have been able to supplement federal funds through royalty revenues from patent licenses).

177. *See, e.g.*, Notice, 59 Fed. Reg. 35,939 (1994) (solicitation by DHH for genotech or pharma participant in CRADA for the biomedical use of novel approaches for lentivirus vaccine development, with the aims of rapid publication of research results and timely commercialization); Notice, 59 Fed. Reg. 35,938 (1994) (solicitation by DHHS and the National Cancer Institutes for genotech or pharma participant in CRADA for the biomedical use of novel approaches for HIV-1 Vaccine Development); *see also* 37 C.F.R. § 401.1-.16 (1987) (recognizing rights to inventions made by not-for-profit organizations and small business firms under government grants and cooperative agreements).

178. Special assessments and intellectual property protection must be considered when negotiating with foreign individuals and governments.

information derived during the resulting cooperative research. Moreover, all federal agencies are "taxed" to support the Federal Laboratory Consortium, an interagency group which helps to resolve technology transfer issues raised between government agencies, as well as CRADAs.[179]

The NIH[180] and DOE,[181] two of the three major institutions funding the HGP[182] have made extensive use of their authority to enter into CRADAs with the private sector, thereby advancing genotechnology in the field of human genetics.[183] DOE laboratories have entered into over 300 CRADAs while the NIH Office of Technology Transfer encourages and licenses the development of technology at its GOCO laboratories.[184] Moreover, DOE and NIH foster technology transfers by actively seeking applicants for Small Business Innovation Research (SBIR) grants.[185]

CRADAs have been criticized for, among other things, allegedly creating an unfair advantage for former government researchers both directly and through added responsiveness at the regulatory (PTO, NIH and FDA) levels.[186] Private firms also have alleged that they have less influence than

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179. Day, *supra* note 90, at 19. Currently, there is a revived proposal to establish a cabinet-level Science Department to coordinate R&D programs among federal agencies. *See* Graeme Browning, *Tense Days Down in the Lab*, NAT'L L.J., Apr. 22, 1995, at 1005; *infra* notes 231 and accompanying text.

180. NIH is the principle biomedical and behavioral research agency within the federal government, and its mission is to improve human health by increasing scientific knowledge related to health and disease through biomedical and behavioral research.

181. HGP actually was initiated by Dr. Charles DeLisi, the former director of DOE's health and environment research programs. DiChristina, *supra* note 24, at 16.

182. The other major contributor to the HGP is the Howard Hughes Medical Institute.

183. *See* DAN BERGLUND & CHRISTOPHER COBURN, PARTNERSHIPS: A COMPENDIUM OF STATE AND FEDERAL COOPERATIVE TECHNOLOGY PROGRAMS 219, 486-91, 513-19, 521-22, 523-24, 548-53 (1995); *Rudolph, supra* note 171; *Small Business Innovation Research (SBIR) Grants*, HUM. GENOME NEWS, May-June 1995, at 15; *see also NIH Should Rethink Pricing Clause*, 372 NATURE 488 (1994). The federal transfer policy was at the center of a major pricing clause controversy. The clause at issue allowed NIH to set "reasonable prices" for products developed jointly with industry. This clause was introduced out of anger over the cost of AZT, an AIDS drug, which was furthered by work done in NIH laboratories. Because the clause was reputed to discourage investment by venture capitalists in companies that enter into CRADAs, NIH was urged by various members of its advisory councils to drop it, and did so. *Id.*

184. Rudolph, *supra* note 171, at 142. The policy implications of CRADAs are addressed fully *supra* Section II and *infra* Section III. The NIH recently announced that it will monitor recipients that conduct studies for private industry more closely and hold agencies back from imposing entanglements. *See* David E. Bartlett, *NIH Regulations Now Guide Sponsored Research*, NAT'L L.J., Oct. 23, 1995, at C46.

185. *Small Business Innovation Research (SBIR) Grants*, *supra* note 183, at 15.

186. *See* Victoria Slind-Flor, *Biotech Patent Derided: Critics Say It's Overbroad and Will Hinder the Search for Treatment of AIDS*, NAT.'L L. J., Apr. 10, 1995, at A6; *see infra* notes 348 and accompanying text (addressing patent granted on Mar. 21, 1995, to Dr. W. French Anderson and his colleagues at the NIH, which "covers any method of introducing genetically altered human cells into a patient to combat disease"). This controversy is likely to continue, for career shifts from government service to genotechnology by top researchers are common. For example, David J. Galas, Darwin Molecular's president and chief scientific officer, previously

they desire in setting the research agenda and must abide by complicated rules about conflicts of interest and property rights of research results.[187] Nevertheless, the popularity of using federally-owned technology to foster human health benefits while promoting economic competitiveness and growth is evident in the hundreds of measures introduced in Congress in each of the last few sessions which would affect technology transfer.[188] These measures include proposals to coordinate all federal transfers of technology and federal investment in the area of genotechnology.[189]

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ran HGP. *See* Rosenberg, *supra* note 155, at 80-81; *see generally, supra* Section II.

187. Rudolph, *supra* note 171, at 142.

188. Giving away federally-owned technology to promote economic competitiveness and growth is a popular notion within Congress. "Congress is constantly tinkering with the laws governing technology transfer. In the last Congress, 80 bills were introduced that referenced or amended the Stevenson-Wydler Act, among 243 measures introduced that somehow affected technology transfer." Rudolph, *supra* note 171, at 133 (completely addresses all federally supported R&D) (discusses H.R. 820, H.R. 1432, and H.R. 523, which are identified as "noteworthy"). H.R. 820 contains the National Competitiveness Act of 1993, the Manufacturing Technology and Extension Act of 1993, and the Civilian Technology Development Act of 1993. "These proposals seek to boost the nation's international competitiveness by strengthening our technology base and fostering the development of advanced products, particularly in manufacturing." *Id.*

189. *See* Rudolph, *supra* note 171; *see also* Browning, *supra* note 179, at 1005; Eliot Marshall, *Data Sharing: A Declining Ethic*, 248 SCIENCE 952 (1990). Among these proposals are the following:

> · Federal Technology Commercialization and Credit Enhancement Act of 1995, H.R. 80, 104th Cong., 1st Sess. (1995): A bill "[t]o foster economic growth, create new employment opportunities, and strengthen the industrial base of the United States by providing credit for businesses and by facilitating the transfer and commercialization of government-owned patents, licenses, processes, and technologies, and for other purposes." The stated objectives are to: provide financing to private sector to commercialize the technologies; develop centralized database; plan to finance by taxing foreign corporations; and establish an independent corporation to administer some $3,000,000,000.
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> · Developing Sponsored Research Agreements, 59 Fed. Reg. 55673 (1994): A draft agreement, introduced by NIH, for use by recipients of NIH funding. The main concern expressed by the NIH in this proposal is that recipients of NIH funds comply with the funding agreement requirements so that information produced under the CRADA is disseminated to industry as per the requirements of the Act and implementing regulations.
>
> · Uniform Biological Material Transfer Agreement, 60 Fed. Reg. 12771 (1995): Proposal sponsored by the Department of Health and Human Services and NIH for a Uniform Biological Material Transfer Agreement (UBTMA) This agreement was designed for use when material is transferred between not-for-profit organizations for research. It does not address transfer between universities and industry, because such transfers essentially are license agreements for which universities have standard-form agreements. Under this proposal, (1) such material may be used only for teaching or academic purposes; (2) the recipients of the transferred material have unchecked rights to distribute the substances created only if such a substance is not a progeny, modification, or unmodified derivative; and (3) the material must be

2. *Patents and Genotechnology*

Another fundamental example of the federal government's desire to advance genotechnology is its willingness to recognize and protect intellectual property rights[190] in technological advancements.[191] Although United States

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provided at no cost. The predecessors of this proposal are the "Policy Relating to Distribution of Unique Research Resources Produced with PHS Funding" issued by the PHS in 1988 and PHS's adoption in 1989 of a standard Material Transfer Agreement form for use by PHS scientists.

· 37 C.F.R. Ch. IV, §§ 404.1-.14: Department of Commerce policy to use the patent system to promote the utilization of inventions arising from federally supported research or development.

· H.R. 632, 104th Cong., 1st Sess. (1995): A proposal to increase fairness in the compensation of patent owners whose patented inventions are used by the United States government.

See also Bill Mandating Transfer of Patient's Rights from Federal Labs is Reintroduced, 50 PAT. TRADEMARK & COPYRIGHT J. (BNA) 369 (Aug. 10, 1995) (summarizing provisions of H.R. 2196 which would amend Stevenson-Wydler Act by, *inter alia*, directing federal labs to assign any intellectual property rights resulting from work done under CRADA to the private sector partner and government to retain paid-up irrevocable license and "march-in" rights if holder of intellectual property rights fails to commercialize technology).

190. This section concentrates on United States patent policy. Copyright may apply to certain outputs of the genotech companies' work, including written documentation, computer programs and databases. However, the scope of protection afforded under copyright law may vary depending on the nature of the output. In particular, copyright is unlikely to afford meaningful protection to gene sequences for three reasons. *First*, for a work to be eligible for copyright protection, it must be "original." 17 U.S.C. § 102(a) (1988 & Supp. V 1993). The Supreme Court has interpreted originality to require some modicum of creativity. Mere mechanical listings of gene sequences, whether in hard-copy form or stored in a computer database, are unlikely to meet the originality requirement. *See* Oman, *Biotech Patenting Issues*, *supra* note 13, at C43-44. *Second*, it is a long-standing doctrine of copyright law that copyright protects only expressions of ideas, not the ideas themselves: "In no case does copyright protection for an original work of authorship extend to any idea, procedure, process, system, method of operation, concept, principle, or discovery, regardless of the form in which it is described, explained, illustrated, or embodied in such work." 17 U.S.C. § 102(b) (1988). Genetic code may be regarded as an idea or discovery which, if protectable at all, must meet the rigorous requirements of the Patent Act. *Third*, closely related to the textual language of § 102(b) is the judicial gloss of "merger." According to the merger doctrine, where there is only one or a very limited number of ways to express an idea, the expression merges with the idea and no copyright protection is available. *See, e.g.*, Computer Assocs. Int'l, Inc. v. Altai, Inc., 982 F.2d 693, 707-08 (2d Cir. 1992). Even if genetic code can be copyrighted, its expression may merge with the idea and therefore be unprotectable if it can be precisely described in only one way. *See* Oman, *supra* note 13, at C43; Seide & Smith, *supra* note 1, at 58 (footnote omitted) (Copyright Office indicating it will not register copyrights in DNA sequences).

Note, however, that state trade secret law may provide an avenue of protection for genotech firms. In contrast to the patent system, which requires disclosure of a discovery prior to an inventor receiving a patent, trade secret protection inheres in data only so long as that data is kept secret. The congressional willingness to grant patents in genotech-related inventions, as well as to consider lowering the traditional patent threshold requirements for protection, may be motivated in part by a desire to provide an incentive for inventors to seek patent protection through

law historically has accorded patent protection to inventions meeting statutory standards,[192] United States patent practice in the genotech area has created domestic and international controversy. The policy has been opposed vigorously by other countries[193] and by groups within the United States as disparate as the scientific and religious communities.[194] Although it is premature to assess with certainty the extent to which genotech-related United States patents will be upheld by the courts, patent practice is affecting the shape of the industry. Moreover, there is an obvious need for reforms to minimize investor uncertainty and to optimize innovation in the field of genotechnology.

The opposition to patenting genotech-related inventions has been grounded in economics, law and ethics. The willingness of the United States to encourage patent applications[195] and issue patents has generated concern on the part of other nations. Many fear that the United States will "corner the market" on genotech, thereby increasing industry entrance costs to foreign firms due to the necessity of their licensing technology from American firms or seeking funding from their own governments.[196] American patent practice also has engendered global uneasiness about the propriety of (1) patenting human life forms and (2) competition among countries, rather than cooperation, for information which has the potential to save and improve countless lives.[197]

The controversy over patenting genotech inventions exploded in 1991 when the NIH attempted to patent certain identified gene sequences discovered by Dr. Craig Venter, then an NIH researcher. The NIH claimed 351 partial cDNA fragments in its initial application and later filed claims to over 2750

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concomitant disclosure rather than relying on trade secret. Thus, patent protection may make more information available to the public and other researchers than would reliance on trade secret law. *See infra* note 382 and accompanying text.

191. *See infra* note 349 (Genetic Therapy Inc. obtained a broad patent in April 1995 for one form of gene therapy.).

192. The first United States patent statute was enacted in 1790. Major revisions were enacted in 1836 and 1952. Recently, major changes have been enacted and proposed to bring the United States into compliance with the General Agreement on Tariffs and Trade (GATT). For an excellent overview of the history of patent law, see ROBERT PATRICK MERGES, PATENT LAW AND POLICY 1-9 (1992). *See also infra* notes 364-67 and accompanying text for a discussion of the statutory standards.

193. *See, e.g.*, Kirby, *supra* note 33, at 11 (conflict over recognizing property interests in genome discoveries); *infra* text accompanying notes 212-13.

194. *See infra* text accompanying notes 214 and 414.

195. The United States leads the world in genotech patent applications and thus, potentially, in issued patents. Kirby, *supra* note 33, at 17 (over 35,000 patent applications for biological materials filed in United States compared to about 13,000 in Europe).

196. *See supra* note 2 (noting that outside the United States, genotech R&D often is conducted in collaboration with United States genotech firms). However, note that government subsidization has characterized the genotech industry within the United States as well as abroad.

197. *See infra* text accompanying notes 212-14.

partial cDNA sequences.[198] These patent applications were filed despite the fact that researchers had not identified the genes' structures or functions.[199] The NIH's stated intentions were: (1) to encourage commercial applications of its research by licensing the data to private commercial entities at a nominal fee, thereby giving them an incentive to develop new drugs and (2) to avoid situations where several companies own a segment of a complete gene, thus requiring complex cross-licensing in the event that any of these companies wished to commercialize the entire gene or its particular product.[200]

Regardless of the NIH's intentions, the filings outraged members of both the scientific and international communities. Renowned scientist James Watson, co-discoverer of the DNA double helix and then director of the NIH's HGP project, argued that patenting the "secrets of life" would hinder research.[201] He also emphasized that gene sequences, like the double helix, should be available for all humanity.[202] Many members of the international community consider the NIH's filings to be shortsighted and contradictory to HGP:

> Ironically, the very country that founded the HGP and recognized its essential international character sponsored patent applications that inflamed those whose cooperation was essential to completion of the project . . . . Many countries have specific provisions barring the grant of patents for innovations whose publication or exploitation would be contrary to morality.[203]

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198. Smith & Kettelberger, *supra* note 151, at 46.

199. *Id.*

200. *Id.* at 46-47 (noting that another force encouraging NIH to file was fear that prior publication would destroy potential foreign patent rights). *But see* Christopher A. Michaels, *Biotechnology and the Requirement for Utility in Patent Law*, 76 J. PAT. & TRADEMARK OFF. SOC'Y 247, 248 (1994) (noting that, within government itself, patenting gene sequences is controversial: "The National Research Council Committee on Mapping and Sequencing the Human Genome concluded in its 1988 study that 'human genome sequences should be a public trust' not subject to the intellectual property laws, while the Office of Technology Assessment's 1988 report on the Genome Project suggested that federal agencies and Congress should instead promote early filing of patent applications followed by prompt release of data").

201. Smith & Kettelberger, *supra* note 151, at 47; Bylinsky, *supra* note 8, at 100. Watson resigned from the NIH shortly after the patent controversy erupted. The reasons for his resignation are unclear. *See The Genome Project: Will It Be Allowed to Survive?*, NEWSDAY, May 19, 1992, at 61 (Watson left after Dr. Bernadine Healy, then director of the NIH, "raised questions about Watson's ownership of biotechnology company stocks . . . [Healy] did deny in the journal, *Science*, that she had used conflict of interest allegations to force Watson's resignation. Watson's friends are convinced she wanted him out because of bitter disagreement over the NIH's new policy of seeking patents.").

202. Kirby, *supra* note 33, at 17; Bylinsky, *supra* note 8, at 100.

203. Kirby, *supra* note 33, at 11, 17 (noting also that patent applications undermined the principle of international cooperation, and the subject led to "many an angry clash" among participants at the May 1993 conference in Balboa, Spain).

Individual nations have also spoken out against the NIH's actions. France accused the United States of placing HGP at risk by penalizing low-budget research efforts and increasing the overall cost of the Project.[204] France also raised ethical objections, contending that patents should not be issued on something that is "part of our universal heritage."[205] Similarly, Italy opined that the NIH decision would undermine the HGP by encouraging competition for patents.[206] Italy also objected on substantive legal grounds, contending that an invention setting forth partial gene sequences of unknown function fails to meet standard threshold requirements for patentable inventions.[207] On the other hand, countries such as Great Britain reacted by rushing to file their own patents.[208]

The NIH patent applications were rejected by the PTO[209] and later withdrawn by the NIH.[210] The most widely voiced legal objection to the NIH patents was that the NIH did not know what functions the gene sequences performed and that, therefore, the inventions lacked utility as required under the Patent Act.[211]

The NIH filing controversy highlighted the differences between the patent policies of the United States and European nations that are visible in Article 53(a) of the European Patent Convention. Article 53(a) prohibits granting patents for inventions whose publication or exploitation would be contrary to public policy or morality.[212] Moreover, the European Parliament recently vetoed European Union (EU) legislation aimed at making the EU genotech industry more competitive with that in the United States and Japan. The legislation would have clarified the conditions under which genes could be patented.[213] There is no doctrine under United States law that is comparable

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204. Smith & Kettelberger, *supra* note 151, at 47.

205. *Id.*

206. *Id.* at 48.

207. *Id.*

208. *Id.*

209. *Id.* at 57 (rejection based on failure of claims to meet statutory standards: partial gene sequences not new, useful or nonobvious, and no enabling disclosure provided); *see also infra* Section III.B.2.

210. Christopher Anderson, *NIH Drops Bid for Gene Patients*, 263 SCIENCE 909 (1994).

211. 35 U.S.C. § 101 (1988 & Supp. V 1993); *see also infra* text accompanying notes 364-67 (discussion of utility requirement). In its applications, NIH cited the following utilities for the gene sequences: "to (1) map chromosomes; (2) identify tissue types . . . ; and (3) identify gene regions associated with a disease." MERGES, *supra* note 192, at 159; *cf. infra* notes 377-78 and accompanying text (arguing that strongest legal objection should be that gene sequences are "phenomena of nature" and a non-patentable discovery rather than a patentable invention).

212. John Richards, *International Aspects of Patent Protection for Biotechnology*, 4 FORDHAM INTELL. PROP. MEDIA & ENT. L. J. 433, 443 (1993).

213. Specifically, the European Parliament:

> invoked new powers on March 1 to veto European Union legislation on gene patents. Supporters of the proposals by the executive European Commission claimed that the veto . . . could harm the competitiveness of Europe's biotechnology industry. They argued that

to Article 53(a), although religious leaders have raised strong public policy objections to patenting human life forms.[214]

Despite objections to United States patent policy from abroad and at home, the United States government has remained committed to advancing genotechnology through the recognition of intellectual property rights. For example, Congress has enacted legislation to bring the United States into compliance with the General Agreement on Tariffs and Trade (GATT). The legislation seeks to assist in maintaining the viability of genotech patents.[215] Furthermore, the United States was reluctant to sign the Convention on Biological Diversity without an interpretive statement,[216] and the President recently signed legislation making it easier for genotech firms to obtain process

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> absence of EU legislation laying down conditions under which genes could be patented would play into the hands of rival researchers in the United States and Japan . . . . Parliamentary officials said it was the first time the assembly had used the rights granted it in the Maastricht Treaty to reject a legislative proposal in its entirety under new "co-decision" procedures . . . .

European Parliament Blocks EU Rules On Patents for Biotechnology Products, 9 WORLD INTELL. PROP REP. 96, 96-97 (1995). National patents and European patents through the European Patent Office may, however, still be available. *Id.* at 97.

214. *See infra* note 414 (describing objections raised by religious leaders); *cf.* Robert P. Merges, *Intellectual Property in Higher Life Forms: The Patent System and Controversial Technologies*, 47 MD. L. REV. 1051, 1067 (1988) (arguing that new technologies should not be denied patent protection merely on speculation about consequences and that the patent system is not where technology evaluation should occur). Nevertheless, American courts historically have been willing to withhold patents on inventions considered immoral, such as gambling machines and inventions used to defraud. *Id.* at 1062.

215. *Legislation: GATT Bill Clears House with Major Intellectual Property Law Reforms*, 49 PAT. TRADEMARK & COPYRIGHT J. (BNA) 95 (1994). Under prior United States law, the term of a patent was 17 years from the date of issuance. *Id.* Under GATT, it is 20 years from the date of filing. *Id.* Because many applications, including those associated with genotech, often take in excess of three years to find their way through the PTO, a number of firms, including genotech firms, were concerned that compliance with GATT would effectively shorten their patent protection. *Id.* To address this concern over lag time between application and patent issuance, a provision was inserted into the implementing legislation to extend a patent term if the patent's issuance is delayed by interference proceedings, a government secrecy order, or by appeals to the Board of Patent Appeals and Interferences or the Federal Circuit. *Id.* at 95. Such extensions may be up to five years. *Id.* at 96.

216. Karen Anne Goldman, Note, *Compensation for Use of Biological Resources Under the Convention on Biological Diversity: Compatibility of Conservation Measures and Competitiveness of the Biotechnology Industry*, 25 LAW & POL'Y INT'L BUS. 695 (1994) (United States refused to sign Biodiversity Convention for one year because of economic provisions requiring direct financing or exchange of resources and technology, including compensation to developing countries for use of biological resources.); *cf.* Ralph T. King, Jr., *Grace's Patent on a Pesticide Enrages Indians*, WALL ST. J., Sept. 13, 1995, at B1, B9 (coalition of 200 organizations from 35 countries challenging a W. R. Grace & Co. process patent for pesticide development based on a formulation from seeds of the Indian neem tree, claiming, "intellectual and biological piracy." At the same time, however, Shaman Pharmaceuticals, Inc. seems to have adopted a policy of compensating those countries which it prospects for materials for gene therapy through up-front payments and contributions of future profits to a foundation for rain-forest preservation.).

patents.[217]

3. *The Orphan Drug Act*

Another source of market protection available for many of the forthcoming genotech-based drugs—many of which are characterized as "biologics" (drugs premised on altering or influencing genes)[218]—is the Orphan Drug Act. This legislation gives companies working on drugs for "rare diseases and conditions" control over their target markets, making the development of such drugs more economically worthwhile.[219] The first applicant to obtain such designation and approval of a marketing application for a drug is entitled to market exclusivity for a period of seven years.[220] Moreover, the developers of such drugs receive a fifty percent tax credit and may request federal grants to offset testing expenses incurred in drug development.[221]

Although the Orphan Drug Act protects markets to encourage drug development, it has been criticized by members of the genotech community and others as helping individual companies at the expense of the overall industry. Critics argue that the actual markets for such drugs are much larger than anticipated because the drugs' initial potentials are often underestimated, and that markets may continue to grow through subsequently discovered uses.[222] Another criticism is that it is possible for a drug developer intentionally to define its "target" market narrowly enough to obtain the designation, with full knowledge that the actual market is much larger and that physicians will prescribe the drug for other known uses. Raising this and related market concerns, some activists for AIDS sufferers claim that this

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217. *President Clinton Signs Bills on Biotech Patents, Performance Rights*, 51 PAT. TRADEMARK & COPYRIGHT J. (BNA) 45 (1995) (legislation amends 35 U.S.C. § 103 by "prohibiting obviousness rejections of process patent applications for biotechnological processes 'using or resulting' in a composition of matter which is novel and non-obvious if: (1) the product and process claims are in the same application and have the same filing date; and (2) the product and process claims were owned by the same person when they were invented.").

218. *See infra* notes 234, 243-44 and accompanying text.

219. Orphan Drug Amendment of 1988, Pub. L. No. 100-290, § 3, 102 Stat. 90 (1988) (codified at 21 U.S.C. §§ 301, 360aa, 360bb, 360ee (1988)); 42 U.S.C. § 236 (1988). *See generally* Veronica Henry, *Problems With Pharmaceutical Regulation in the United States*, 14 J. LEGAL MED. 617 (1993); Malinowski, *supra* note 89, at 8, n.13.

220. In other words, no other company can market a molecularly identical orphan drug for FDA-approved use for seven years after that approval is granted.

221. The applicability of this credit is, however, limited by three factors: (1) the tax credit applies only to expenses incurred in clinical trials on humans, not preclinical testing expense; (2) the credit cannot be reaquired, and the company only benefits if it can afford to take advantage of the credit; and (3) the company must be continually "carrying on business." The third limitation makes it difficult for biotechnology companies, making very little profit and accordingly not marketing products until many years after start up. Henry, *supra* note 219, at 636.

222. *Id.* at 632.

market exclusivity has led to monopoly pricing.[223]

"Orphan drug" designation is granted by the FDA for rare diseases, which include numerous genetic diseases. Many of the products being developed by the genotech industry may qualify as orphan drugs. Designating them as such will benefit their individual developers and may indirectly help the entire industry by bringing about market successes that lure investors. Despite such purported benefits, since 1993, BIO, the biotechnology industry's trade association, has been seeking to limit the market protection allotted under the Act. The organization drafted a proposal to limit the market exclusivity of such drugs to five years with a provision allowing the sponsors of products with "limited commercial potential" to apply for five-year extensions.[224] Also, while the Pharmaceutical Manufacturers Association wants to keep the Orphan Drug Act as it is, the National Organization for Rare Disorders (NORD) has supported a bill that would protect markets either for seven years or until $200 million in cumulative sales has been realized, whichever comes first.[225]

Recent developments suggest that amendments to the Orphan Drug Act are likely. In 1994, Congress proposed amending the orphan drug rules to reduce the period of market exclusivity from seven to four years, with an opportunity to extend exclusivity for an additional three years for drugs that are of limited commercial potential.[226] This proposed legislation also would allow companies to share exclusivity if they develop a drug independently but simultaneously.[227]

C. *National Institutes of Health Funding*

As stated by one commentator, "[i]n a very real sense, NIH is the father of the biotechnology industry in the United States."[228] Beyond its involvement in administering HGP, the NIH conducts its own research[229] and sponsors billions of dollars worth of research annually at universities and other public and private institutions.[230] In other words, the NIH is to the genotech

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223. Note, however, that the kinds of drugs which the Orphan Drug Act applies to carried prices higher than average even prior to the passage of the Act. *Id.* at 635-36.

224. *Id.* at 636.

225. *Id.*

226. *See* BIOTECH 95, *supra* note 2, at 14.

227. *Id.*

228. Thomas O. McGarity, *Peer Review in Awarding Federal Grants in the Arts and Sciences*, 9 HIGH TECH. L.J. 1, 7 (1995).

229. *Id.* NIH transfers many of the resulting discoveries to private industry for commercialization. *See supra* Section II.B.1.

230. McGarity, *supra* note 228, at 7-8. "Americans have been generous to their biomedical researchers. For more than 30 years, large fees for hospital treatment have supported the development of many new techniques. At the same time, the budget of the National Institutes of

industry what NASA has been to the space mission. However, unlike NASA's, NIH's funding is secure—at least for the time being.[231] With an annual budget of almost $7 billion, NIH supports "more than 25,000 separate awards in health and environmental sciences."[232]

The NIH oversees human clinical trials, including those involving genotech-based therapeutics and diagnostics. Although the FDA is directly responsible for review of genotechnology applications,[233] it is collaborating with the NIH to combine and accelerate review of gene therapy protocols.[234]

The NIH's involvement in the genotech industry also has caused immense controversy as evidenced by the patent dispute discussed above.[235] The NIH also became involved in a pricing controversy triggered by the marketing of AZT.[236] These controversies demonstrate that the NIH's actions can profoundly affect the genotech industry—negatively and positively—and, therefore, its decisions and policies must be crafted with both foresight and caution.[237]

Health, which supports 70% of American academic medical research, has climbed steadily." *Managing to Care*, THE ECONOMIST, Sept. 23, 1995, at 75.

231. In 1994, the NIH budget included an 18% increase (to $152 million) for the National Center for Human Genome Research. BIOTECH 95, *supra* note 2, at 15. Although recently there was a proposal to cut NIH's budget by $7.9 billion, the Senate quickly restored $7 billion, thereby essentially singling out the NIH and sparing it from the wide blade of Congressional budget cuts. *See* Richard Saltus, *NIH Wins Support on Funding in Senate*, BOSTON GLOBE, May 25, 1995, at 11 (NIH spared from present budget cuts, at least relative to most other agencies). HGP's budget for 1996 presently is expected to be reduced only by $1 million. *Supra* note 85. *But see* Anthony Flint, *Universities Face New Era in Research Funding*, BOSTON GLOBE, June 19, 1995, at 1, 6 (addressing "slashing" of federal funds designated for research, addressing the question "why not have Dow or Merck pay for the work instead of Uncle Sam?" and considering the possibility that teaching institutions will be transformed into corporate R&D centers); Lovejoy, *supra* note 1 (highlighting the expansive potential of genotechnology and stating that "[t]his potential could be jeopardized, however, by . . . [b]udget cuts that could slow advances in biotechnology, where the U.S. leads all other nations"); Browning, *supra* note 179, at 1005 (noting that the federal government funds 36% of research and development in United States; and that new Congress may reduce funding for projects with reasonable expectation of private sector financing).

232. *See* McGarity, *supra* note 228, at 7.

233. *See infra* Section II.D.

234. *See Prescription Drug User Fee Act of 1992*, Pub. L. No. 102-571, 106 Stat. 4491; BIOTECH 95, *supra* note 2, at 14-15. Biologics were regulated before other drugs, and that responsibility originally rested with NIH. Now the FDA and NIH work together on biologics through the Center for Biological Evaluation and Research (CBER), which is under the jurisdiction of the FDA, as discussed *infra* Section II.D.1.

235. *See supra* notes 198-211 and accompanying text.

236. *See supra* note 183 and accompanying text (addressing the CRADA "reasonable price" clause controversy).

237. There is some evidence that the NIH is reassessing its policies, particularly with respect to gene therapy. *See* Gorman, *supra* note 16, at 63. The head of NIH "appointed an independent committee of scientists to look into how the NIH spends its gene-therapy research dollars (some $200 million a year) and whether the government is getting its money's worth." *Id.*

D. *Food and Drug Administration Regulation*

The United States has "the most demanding prescription drug approval regimens in the world."[238] The time from discovery and cloning of a new molecule to market entry for a resulting drug—the aforementioned "drug lag"—is seven to twelve years, and the process of getting to market often costs as much as $400 million.[239] Beyond institutional sluggishness within the process, "[t]he reasons for delay include errors in pharmaceutical industry practice, lack of cooperation between the pharmaceutical industry and the FDA, misdirected research, poor investigative data, and excessive bureaucratic procedure."[240] Moreover, "[f]or every 10,000 drug candidates created in the lab, only 1,000 compounds will be tested in animals" and, of those, only one will reach the market. Human testing itself is a two to four year process, and only twenty percent of the compounds tested in humans will reach the market.[241]

All new drugs, including biologics, are subject to regulation under the Federal Food, Drug, and Cosmetic Act (FDCA).[242] Biologics and their developers and manufacturers are also subject to further requirements under the Public Health Service Act (PHSA).[243] The primary objective of the FDCA is to ensure the safety and effectiveness of the final product, with controlling the manufacturing process a secondary concern. In contrast, biologics regulation under the PHSA is focused on "rigid control of the

238. Henry, *supra* note 219, at 617.

239. *See* Fisher, *supra* note 7, at B3; Eric D. Randall, *Genetics Research Carries Risks*, U.S.A. TODAY, Mar. 22, 1994, at 3B (stating that the development of drugs based upon identified genes takes four to six years). "Researchers at large pharmaceutical companies screen thousands of compounds in trial-and-error 'grind and find' tests before finally hitting on a promising drug—typically spending $400 million and 12 years in the process." Helm, *supra* note 75, at D1.

240. Henry, *supra* note 219, at 623.

241. *Id.* at 617.

242. *See* JAMES T. O'REILLY, FOOD AND DRUG ADMINISTRATION §§ 13-15 (2nd ed. 1993).

243. Public Health and Service Act, Pub. L. No. 57-244, 58 Stat. 682, 702-03 (1944) (codified at 42 U.S.C. § 262 (1988)). The added burdens for biologics have included requirements that (1) the product used in the Phase III trials generally must be produced in the intended commercial-scale manufacturing facility; (2) only the company that manufacturers the biologic may obtain and hold the marketing licenses; and (3) each significant participant in the manufacturing process must hold establishment and product licenses for the new technology. According to some commentators, the divergent regulatory emphasis of the PHSA (manufacturing process) and the FDCA (safety of final process) reflects the assumptions of a time "when biologics were crude mixtures or biological extracts." Gary E. Gamerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 FOOD & DRUG L.J. 213, 213 (1994). As stated by one commentator, "[t]he establishment licensure requirement, in particular, creates for biologics manufacturers significant and costly commercial and legal problems that drain financial resources and competitiveness, and impedes the use of improved manufacturing technologies and strategies." *Id.* at 214. This distinction between biologics and other drugs is discussed in more detail *infra* Section III.A.

manufacturing process," which reflects the particular scientific and historical characteristics of biopharmaceuticals.[244]

1. *The Drug-Approval Process*

As stated above, both the FDCA and the PHSA, and their implementing regulations, govern the testing (for efficacy and safety), manufacturing, and marketing of biologics and new drugs.[245] Within the FDA, the Center for Drug Evaluation and Research (CDER) regulates new drugs, while new biologics are regulated by the Center for Biological Evaluation and Research (CBER).[246] Genetic therapeutics are subject to added regulatory clearance requirements prior to clinical trials and commercialization, and the novelty of these technologies requires the FDA to review each protocol on a case-by-case basis.[247]

Diagnostics are regulated separately as "medical devices" and "testing kits."[248] Because of their complexity, genetics-based diagnostics generally are labelled Class III devices. A Class III device requires pre-market approval unless its manufacturer can demonstrate that the device is the substantial equivalent of an existing Class I or II device,[249] or a pre-1976 device not yet classified.[250] Accordingly, the burden on the developers and manufacturers of genetics-based diagnostics is comparable to that for developers of new drugs. They must perform clinical studies, obtain an investigational device exemption to conduct clinical tests, file a pre-market approval application, and ultimately obtain FDA approval.

The approval process traditionally consists of a preclinical phase, followed by three phases of trials on human subjects and a review phase. The process is summarized in Table I:

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244. Gamerman, *supra* note 243, at 213.

245. *See generally* O'REILLY, *supra* note 242, at § 13-15.

246. *See generally id.*

247. *See supra* note 243 (addressing added requirements). The FDA has published a "Points to Consider" guidance document to help develop gene therapy protocols.

248. O'REILLY, *supra* note 242, at § 18.02.

249. Establishing substantial equivalence to a Class I device requires adherence to *general* controls associated with that device, and substantial equivalence to a Class II device mandates adherence to *general and special* controls. Manufacturers of new devices also may have to conduct clinical tests to demonstrate that differences between the new and existing devices do not affect safety or effectiveness. *See* O'REILLY, *supra* note 242, at § 18.04.

250. Pre-1976 devices not yet classified are viewed as having proven efficacy because of the longevity of their use.

TABLE I:[251]

FDA Review Process for Biotech Products

PHASE	TEST	PURPOSE	TIME FRAME (YEARS)	SUCCESS RATE
PRECLINICAL	Laboratory and Animal Studies	Assess Safety and Biological Activity	1.8	10%
IND APPLICATIONS				
I	20 to 80 healthy volunteers	Evaluate Safety and Dosage	.5	30%
II	100 to 300 patient volunteers	Evaluate Effectiveness and Safety	2	67%
III	1000 patient volunteers (approximate)	Verify Effectiveness, Continue Safety Evaluation	3	
IV (FDA REVIEW)		Review All Submitted Data Concerning Safety and Efficacy for Proposed Product	1.7	

251. Table I is compiled in part from data provided by Kendall Strategies Inc. of Cambridge, Massachusetts; additional data was obtained from numerous interviews with representatives from industry and government during the fall of 1995—many resulting from the circulation of earlier drafts of this Article. IND = Investigational New Drug. PLA = Product License Application. ELA = Establishment License Applicator. NDA = New Drug Application.

PLAS and ELAS OR NDAS APPLICATIONS AND REVIEW			2.5 (average; overlap with FDA review)	75% approval (pre-review)
TOTAL			9.8 (min.)	1 out of 10,000 drug candidates

The preclinical phase consists of laboratory work and studies of two or more animal species in order to establish an impact on the target disease and assess side effects and safe dosage ranges.[252] The results of the preclinical phase studies, if promising, become the basis for an Investigational New Drug Application (IND) filed with the FDA. An IND must be granted for drugs to be tested on humans, that is, for Phase I clinical trials to begin and for developers to charge patients for those drugs where the requisite level of efficacy is established.[253] The FDA reviews INDs to assess the design of the proposed studies and to determine whether they will be conducted with safeguards to protect patients.[254]

Phase I clinical trials, which take generally six months to one year, consist of introducing the drug into twenty to eighty healthy human volunteers to determine toxicity, preferred route of administration, and safe dosage range.[255] Of drugs submitted for human clinical trials, seventy percent fail

252. Consider that, because penicillin produces harmful effects in some animals, it might never have reached the market under current FDA regulations.

253. INDs generally consist of (1) a brief introductory statement (identification of the name of the drug, its active ingredients, its pharmacological class, the structural formula, the route of administration, and the drug's broad treatment objectives); (2) an investigational brochure (comprised generally of a summary of the pharmacological and toxicological effects of the drug, its pharmacokinetics, and the resulting biologic disposition in animals); and (3) a clinical trial protocol. *See* O'REILLY, *supra* note 242, at § 13.12.

254. To obtain various objectives (IND approval, clinical trial success, limits on liability, minimization of expense from repeating clinical trials, enhancement of overall negotiation position with FDA) drug developers must select qualified clinical investigators (preferably prestigious teaching hospitals) to supervise administration of the products and ensure investigations are conducted and monitored in accordance with FDA regulations as well as the general investigational plan and protocols contained in the IND. O'REILLY, *supra* note 242, at § 13.11-.12. The present trend among genotech companies is to delegate drug development to contract research organizations (CROs) for clinical process. *See supra* parts II.A, II.B.1. CROs offer economies of scale based upon the expertise in development, clinical trials planning and implementation, feasibility testing, database management, and application procedures realized by CROs. BIOTECH 95, *supra* note 2, at 27.

255. The clinical trial process is discussed fully in O'REILLY, *supra* note 242, at § 13.11-.12.

in Phase I. Phase II trials are conducted on a limited number of human subjects, usually 100 to 300, who have the specific disease or symptoms that the drug is intended to treat. The objective of these Phase I and Phase II trials—which last approximately two years and consist of placebo-controlled, double-blind studies—is to develop dosage and toxicity data and obtain preliminary evidence of effectiveness. They also may address short-term side effects and risks in people whose health is impaired. Of the thirty percent of drugs which reach Phase II, thirty-three percent fail. Thus, there is a total failure rate of approximately eighty percent in Phases I and II.

The remaining twenty percent then undergo Phase III trials which last approximately three years and involve 1000 to 3000 patients. Their objective is to assess the overall risks and benefits of the drug, establish safe and effective dosages, and provide an adequate basis for physician labelling. Finally, in Phase IV of the IND process (actual FDA review), the drugs are evaluated for adverse reactions over time, and the Phase III data is supplemented to address particular concerns and the effects of the drugs on specific groups of subjects.

Before commercialization, if the new therapeutic is a biologic, CBER requires submission and approval of a Product License Application (PLA) and an Establishment License Application (ELA).[256] If classified simply as a new drug, CDER requires the filing of a New Drug Application (NDA). NDAs and PLAs may be filed with the FDA only after the IND process is complete and the requisite data gathered. The FDA, which has 180 days to review a NDA and may request supplemental information, approves about seventy-five percent of all NDAs submitted; approval of PLAs take a comparable amount of time. However, even after a PLA or NDA is approved, the process of reviewing applications takes an average of 2.5 years.

Emphasis on pre-market surveillance and testing, which heavily front-loads drug development costs, distinguishes the United States' drug-approval system from its counterparts in other nations.[257] The practical effects of this approach include enhanced patient safety during drug development and early marketing, added R&D costs,[258] higher capital requirements for drug

256. *See id.*

257. Tufts University conducted a comparative study of drug development between the United States and Great Britain which looked at the drugs approved in these countries between 1977 and 1987. The conclusion reached was that the British system relies more heavily on post-marketing surveillance. *See* Henry, *supra* note 219, at 637-38.

258. *See, e.g.*, Karen Southwick, *Plying a Murky Gene-Therapy Pool Biotechnology: A Promising Field is Hindered by Red Tape, Money*, L.A. TIMES, Mar. 22, 1995, at D4 (The cost of Genzyme's gene therapy trials for its cystic fibrosis therapy "running about $15,000 to $20,000 per patient—more than three times the cost of a conventional trial. And that will translate into high price tags for gene therapy when it is commercially available.").

developers, and delays in drug availability.[259]

2. *Reforms Responsive to the Genotechnology Industry*

During the past few years, genotechnologies with the potential to impact dramatically the lives of terminally-ill patients have reached the FDA in a wave and, not coincidentally, reforms have been enacted to expedite the review process.[260] These reforms are attributable primarily to patient pressure, most notably that applied by AIDS activists and advocates for cancer patients.[261] Congress is currently contemplating an overhaul of the FDA to make it easier for drug and medical device manufacturers to make their products available in the United States' market.[262]

Reforms already implemented have decreased the time of the review process. The FDA and NIH are in the process of accelerating the review of gene therapy protocols by combining their review processes.[263] Under the Prescription Drug User Fee Act of 1992 (PDFA), Congress has added 620 FDA reviewers, 300 in CBER.[264] Moreover, the PDFA introduced a new classification of drugs, which enables the FDA to prioritize new drugs to be reviewed.[265] There is also a safety test agreement among the United States, Europe, and Japan to eliminate duplication of animal testing.[266]

Most important, recent FDA changes shorten time periods and reduce

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259. The recently approved chicken pox vaccine is an illustration of some of the practical effects of the United States' system. Some criticize the FDA's handling of the chicken pox vaccine Varivax because two million children in Europe and Asia have had versions of it since 1984. John Carey, *Is the FDA Hooked on Caution?*, BUSINESS WEEK, Jan. 30, 1995, at 72. A concern which slowed approval of the vaccine was that it is not known how long the vaccine will work and there is a fear that the vaccine could lead to people contracting the disease as adults rather than as children. This is rather problematic, for chicken pox strikes adults with much more serious symptoms. Lawrence K. Altman, *After Long Debate, Vaccine for Chicken Pox is Approved*, N.Y. TIMES, Mar. 18, 1995, at 1.

260. Henry, *supra* note 219, at 639. Carey, *supra* note 259, at 74. ("Some AIDS activists say the [FDA] has been approving some drugs too quickly, without enough clinical testing to figure out the best way to use them, or even if they work.")

261. *See, e.g.*, Peter H. Stone, *Ganging Up on the FDA*, 27 NAT'L J. 410, 414 (1995) (National Kidney Cancer Foundation meeting with trade groups and think tanks to discuss issues and strategies regarding FDA reforms); *see also* Anderson, *Cancer and AIDS Groups Push for Changes in Drug Approval Process*, 81 NAT'L CANCER INST. 829 (1989).

262. This proposal is being initiated through legislation expected to be introduced by Sen. Nancy Kassebaum (R-Kan.), chair of the Senate's Labor and Human Resources Committee. *See* Bloomberg Bus. News, *Bill Would Ease Biotechnology Restrictions*, BOSTON GLOBE, Nov. 5, 1995, at 43.

263. BIOTECH 95, *supra* note 2, at 14-15.

264. Pub. L. No. 102-571, 106 Stat. 4491 (1992).

265. Currently, two mutually exclusive ratings distinguish the therapeutic potentials of drugs—type P (priority) and type S (standard). Type P drugs provide improved treatment over alternative drug therapies through greater effectiveness. *See* Henry, *supra* note 219, at 627.

266. *Id.* at 639.

the number of patients required for testing where technology deals with life-threatening diseases for which there are no alternative treatments available.[267] These changes include (1) the creation of Treatment INDs,[268] (2) the creation of Group C drugs for cancer, and (3) Parallel Drug Tracking[269]—all of which are intended to make investigational drugs available to patients who require them at an earlier time.[270] In November 1995, the Clinton Administration announced FDA reforms expressly intended to maintain American leadership in biotechnology.[271] These reforms include elimination of requirements that genotech companies file separate applications for new drugs and for the manufacturing facilities that will produce them if the drugs are well understood, seek approval for each group of biotech drugs shipped, and file some twenty-one separate applications for each biotech drug approval.[272]

Although there is not an abundance of genotech drugs with full FDA approval,[273] there are signs suggesting that FDA responsiveness is working to speed drugs to market. In December 1994, the FDA approved Genentech's Pulmozyme, a cystic fibrosis therapeutic.[274] This approval came only nine months after the company filed its PLA[275]—about half the usual time—and it was preceded by approval of manufacturing and packaging plans.[276]

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267. *See* 21 CFR § 312.34(b) (1993); 21 U.S.C.A. § 355 (1993); Food Drug Cosm. L. Rep. (CCH) ¶ 71, 187 (Jan. 23, 1995); O'REILLY, *supra* note 242, at §13.13.

268. Treatment INDs, by permitting wider distribution of drugs prior to approval under New Drug application standards, allow patients access to drugs about two to three years earlier than their standard IND counterparts, and the developers of the drugs are allowed to charge patients for their use. Henry, *supra* note 219, at 624. A major problem with Treatment IND's, however, is that, because of their experimental nature, most insurance companies will not cover them. Therefore, "[t]reatment INDs could also set up a two-tiered system whereby wealthy patients would obtain the experimental therapy and those who could not afford the therapy would end up in clinical trials. There is also fear that drug developers may price the investigational drugs too high." *Id.* at 625.

269. Parallel drug tracking makes promising INDs available to selected patients, concurrent with the beginning of clinical trials designed to determine the efficacy of the drug. *Id.* at 625.

270. Henry, *Problems, supra* note 219, at 628 (These regulatory innovations are intended to reduce the mean FDA approval time by 45%, to 5.5 years.).

271. John Schwartz, *FDA Revises Biotechnology Rules*, WASH. POST, Nov. 13, 1995, at A19.

272. *Id.*

273. Rosenberg, *supra* note 87, at 61 (stating that only one new genotech drug earned FDA approval in 1994). *See generally* BIOTECH 96, *supra* note 2.

274. Pulmozyme is a genetically engineered copy of a natural human enzyme which cuts strands of DNA that thicken lung secretions. *See* Fisher, *Cystic Fibrosis Drug Approved*, SAN JOSE MERCURY NEWS, Dec. 30, 1993, at 1A. The drug was approved following a six to nine month clinical trial involving 968 people suffering from cystic fibrosis. *Id.* No tests were performed to assess the drug's safety and effectiveness in children under five years of age or in patients with less than a 40% breathing function, and it also was not tested to see if it would be safe and effective for more than one year. *Id.*

275. BIOTECH 95, *supra* note 2, at 15.

276. Lawrence M. Fisher, *New Drug Approved for Cystic Fibrosis*, LEXINGTON HERALD-LEADER, Dec. 31, 1993, at A3.

Genentech's success with Pulmozyme (and the FDA) is attributed to: (1) early interaction with cystic fibrosis specialists, including scientists associated with the Cystic Fibrosis Foundation and the FDA to identify clinical strategies and data requirements; (2) incorporation of quality-of-life and pharmaceutical measures (the construction of a manufacturing facility and development of a long-range business plan) in Phase II and III studies to avoid having to redo such studies; and (3) establishment of a foundation to help indigent patients—removing the stinger associated with the drug's $10,000 annual per-patient cost[277] and avoiding a pricing controversy like that associated with AZT.[278] The FDA also approved Chiron/Berlex's Betaseron, a drug for multiple sclerosis.[279] In fact, during 1993 and 1994, twenty-four genotech products were approved by the FDA and 234 compounds were in various stages of human testing.[280] During 1995, fifteen genotech products were approved,[281] and 494 products presently are undergoing human clinical trials.[282] (The significant approvals for July 1994 through June 1995 are included in Appendix II.) During the spring of 1995, the FDA announced reforms to speed new therapies—including many of these products—to market.[283]

Accelerating the process even more is FDA's recent willingness to expand access to experimental drugs and perhaps even to forego regulation under certain circumstances. Serono Laboratories Inc. received FDA approval to expand access to Serostim, a genetically engineered human growth hormone for AIDS patients suffering from severe weight loss.[284] The FDA also is

277. Fisher, *supra* note 274, at 1A (stating that the cost could be $10,000 per year).

278. *See supra* note 183 and accompanying text.

279. BIOTECH 95, *supra* note 2, at 16.

280. Rosenberg, *New England Firms Gained Approval for 3 Bio Tech Drugs*, BOSTON GLOBE, Aug. 27, 1995, at 76.

281. BIOTECH 96, *supra* note 2, at 20. Three drugs approved were developed in New England. Rosenberg, *New England Firms, supra* note 280 at 76; *see, e.g., Cambridge Biotech Test*, WALL ST. J., Sept. 13, 1995, at B2 (Cambridge Biotech Corp. received FDA marketing approval for a Human T-Lymphotropic Virus Type I blood-screening test, with an expected annual worldwide market of $30 to $40 million.). It is anticipated that six more genotech products developed in New England will be approved by the FDA in 1996: Avonex, a multiple sclerosis drug produced by Biogen Inc.; Redux, an obesity drug produced by Interneuron Pharmaceuticals Inc.; Graftskin, a natural skin cover for closing venous ulcer wounds, produced by Organogenesis Inc.; Seprafil and Sepracoat, surgical adhesion preventatives produced by Genzyme Corp.; and Serostim, a drug to prevent "AIDS wasting" produced by Serono Laboratories Inc. Ronald Rosenberg, *Biotech Firms Hope 1996 Brings FDA Approvals*, BOSTON GLOBE, Oct. 8, 1995, at 91.

282. BIOTECH 96, *supra* note 2, at 23 (relying upon Goldman Sachs data).

283. *See infra* notes 312-13 and accompanying text (identifying proposed reforms).

284. Ronald Rosenberg, *Serono Wins FDA OK*, BOSTON GLOBE, Dec. 22, 1994, at 47. The trials of this drug have been limited to company-sponsored studies involving approximately 350 individuals. *Id.* Nevertheless, the availability of the drug is demonstrative of willingness by the FDA to expand access if patients are terminally ill.

giving an expedited review to Genzyme's Seprafilm, a technology that reduces the incidence of adhesions after surgery, and which already has been approved for sale in Ireland, Sweden and the Netherlands.[285] Moreover, the FDA will forego immediate regulation of Genzyme's cartilage restoration procedure—in which healthy cartilage is removed, grown and multiplied in a lab, and then transplanted back into the patient—which has been used on about 150 patients in Sweden.[286] Based on the premise that the procedure grows but does not change cells and because of the extensive control procedures Genzyme has already put in place, the FDA is allowing Genzyme to perform the procedure commercially.[287] The relaxation of regulations in cases such as these contributes to the current trend of expanding market access to new products.

E. *Other Examples of Regulatory Support*

There are other federal efforts to bolster investment and R&D in the genotech industry which, though less direct or encompassing than those addressed above, deserve some attention. First, recently enacted federal tax law excludes from taxable income fifty percent of capital gains from certain small business stock,[288] and this law is expected to stimulate investment in genotech firms and other start-up companies.[289] Observers also expect recent SEC Small Business Initiatives limiting restrictions on "seed" financing for private companies to benefit the genotech industry.[290] Furthermore, proposed congressional legislation would limit shareholder actions by creating limited corporate liability for statements and projections labeled "forward-looking."[291] These bills also propose to limit damages in investor fraud class-

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285. *FDA Decision Boosts Genzyme*, BOSTON GLOBE, Aug. 8, 1995, at 45. For reports on the successes of Seprafilm's premarket testing, see *Genzyme Will Seek FDA Approval to Sell Its Seprafilm Product*, WALL ST. J., Sept. 14, 1995, at B2 (Genzyme planning to seek FDA marketing approval for Seprafilm based on favorable test results on gynecological surgery patients); *cf. Genzyme Treatment For Adhesion Helps Half of Trial Patients*, WALL ST. J., Oct. 25, 1995, at B4 (Seprafilm trials resulted in preventing post-surgical adhesions in 51% of colon surgery patients; "less-than-universal effect . . . rais[ing] questions about how widely the treatment may be used if it is approved by the Food and Drug Administration . . . Genzyme has said it hopes Seprafilm will become standard in abdominal and gynecological surgery and create a $400 million to $1 billion market.").

286. Larry Tye, *Genzyme Gets OK to Revive Cartilage-Transplant Trial*, BOSTON GLOBE, Apr. 12, 1995, at 45.

287. Telephone Interview with Mark A. Hofer, General Counsel, Genzyme Corp., Nov. 7, 1995.

288. *See generally* I.R.C. 1202 (1995).

289. Johnson, *supra* note 27, at 10.

290. *Id.* at 11 (analyzing the likely impact of the SEC Small Business Initiative's Regulation D (504), which allows private companies to raise $1 million in a year without standard SEC advertising, investor qualification, or information restrictions).

291. The proposed bills are S. 240 and H.R. 1058, with H.R. 1058 immunizing companies for forward-looking projections and S. 240 having a more moderate requirement of "actual

actions to a portion of the defendant's fault, rather than holding all defendants jointly and severally liable.[292] Such changes would have a noticeable impact on the genotech industry, which has and continues to be plagued with such actions—many inspired by clinical trial failures.[293]

The genotech industry also is likely to benefit from a renewed commitment to promote federal-state partnerships. Many states, including Massachusetts, California and Maryland have targeted developing a genotech industry as a priority.[294] The importance of the industry to those states in which it is concentrated suggests that it will be represented aggressively in federal-state collaborations, especially considering how much these states are doing for the industry.[295] The founding of the State-Federal Technology

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knowledge" that the projection is false. *See* Karen Donovan, *Class Actions Curtailed*, NAT'L L. J., July 10, 1995, at A6.

292. *Id.*

293. *See, e.g.*, Hoexter v. Biogen, Inc., No. 94-12198PBS (D. Mass. filed Nov. 4, 1994) (alleging insider trading in violation of 10(b), 20(a), 20(A), and 10b-5); Lazar v. Vincent, No. 94-12177PBS (D. Mass. filed Nov. 2, 1994) (Biogen, Inc.) (alleges misrepresentations and nondisclosure of material facts regarding Hirulog); Jones v. Biogen, Inc., No. 94-12181PBS (D. Mass. filed Nov. 2, 1994) (allegations of 10(b), 20(a), and 10b-5 violations); Leger v. Perseptive Biosystems, Inc., No. 94-12582PBS (D. Mass. filed Dec. 27, 1994); Vision Sec's v. Perseptive Biosystems, Inc., No. 94-12575PBS (D. Mass. filed Dec. 27, 1994). These suits are all brought on grounds of misrepresentation or failure to disclose material facts under sections 10(b) and 20(a) of the Securities Exchange Acts, (*codified at* 15 U.S.C. §§ 78j(b), 78t(a) (1988)) and under SEC rule 10b-5 (*codified at* 17 C.F.R. §240.10b-5 (1995)).

294. For documentation of Massachusetts' commitment to the biotech industry, *see* Stephen Buckley, Jr. and G. Steven Burrill, BIOTECH 94: NEW ENGLAND (Ernst & Young) (1995); *see also* ANNUAL REPORT, WORC. BUS. DEV. CORP. 3 (1995) (expansion and construction of new biotech research parks in Worcester and Grafton, MA expected); Lissa Eckelbecker, *Building on Biotech: Plans for Two Parks in Grafton Plyg Along as Industry Struggles*, WORCESTER TEL. & GAZETTE, Nov. 6, 1994, at E1 (plans of Tufts University to open Tufts Biotechnology Park). Maryland (with close proximity to NIH and Johns Hopkins University) and California are also attractive to biotech investors. The Bay Area now has more firms—202—than any other region. New England is next with 175. *See* Steve Kaufman, *Bio-Roulette Failures Have Cut the Flow of Funds to Biotech, But Big Rewards Tempt Some Investors*, SAN JOSE MERCURY NEWS, Nov. 28, 1994, at 1D. In the competition to win federal funds, Maryland was designated recently as the home of the AIDS Research Institute, a $12 million package. Co-discoverer of the AIDS virus Robert C. Gallo, epidemiologist William Blattner of the National Cancer Center, and clinician Robert Redfield of the Walter Reed Army Institute of Research will head the Institute. It is anticipated that the Institute will foster Maryland's efforts to become the focus within the genotech industry. *See Baltimore Wins Top AIDS Scientist's Research Institute*, BOSTON GLOBE, May 25, 1995, at 16. *See* Bill Barnhart, *An Improbable Dow Day Industrial, Transportation Indexes Record No Change*, CHIC. TRIB., Jan. 19, 1994, at 5 (addressing California's advantageous entrepreneurial environment for technological innovation). *But see* BIOTECH 95, *supra* note 2, at 15 (several other states are attempting to secure larger biotech investment).

295. A network of state biotechnology associations has formed and is continuing to expand. *See* BIOTECH 96, *supra* note 2, at 44. State and local benefits offered to the industry include: R&D and other investment tax credits; seed captial and/or operating capital funds; tax loss transferability; sales tax exemptions; job creation incentives; investing state pension funds; property tax abatement; subsidized land use tax until facilities are operational; and construction fee waivers. *See id.*

Partnership evidences commitment to an effort to foster a federal-state cooperative approach to technology by promoting collaboration between the White House Office of Science and Technology Policy and the National Governors' Association.[296] Moreover, federal support for the industry and the resulting accomplishments have inspired state efforts and competition to attract the industry's budding businesses.[297]

III. Genotech at the Crossroads: Challenges, Choices, and Proposals for Change

With all of its accomplishments and possibilities, the genotech industry, as it begins to commercialize technologies, is at a proverbial crossroads.[298] In sharp contrast to existing regulatory support for genotech R&D, the legal and regulatory infrastructure to commercialize genotechnologies is lacking. As discussed above, due to financial pressures, the industry has been reshaping itself—a process that has led to dramatic changes.[299] Though genotech now is attracting investment dollars through initial public offerings (IPOs) and other sources,[300] the dry times of 1994 and much of 1995 may have left a lasting impression. There is, or at least should be, awareness that clinical disappointments, public controversy, and short-sighted policymaking to quell the particular controversy of the moment may change the market again.

The following are some of the most important challenges facing the genotech industry, choices before policymakers, and proposals for change. All of these challenges, choices, and proposals bear upon the financial viability of the genotech industry and its attractiveness to investors, which directly affect the future and nature of the industry. Even more important, they also will influence the improvements to human health associated with the forthcoming generation of genotech therapeutics and diagnostics.

A. *The Drug-Approval Process*

The vast majority of the nation's genotech companies, some of which

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296. *See* BERGLUND & COBURN, *supra* note 183, at xiii; *see also* THE STATE - FEDERAL TECHNOLOGY PARTNERSHIP TASK FORCE, FINAL REPORT (1995) (emphasizing the renewal of the National Science and Technology System, state participation, encouragement of private sector investments in technology, and national excellence in manufacturing).

297. *See* Kaufman, *supra* note 294.

298. *See* Day, *supra* note 90, at 18-19 (summarizing and discussing problems: failed tests; lawsuits; impatient investors; precarious reliance on a single-product; cost of publicity).

299. *See generally* BIOTECH 96, *supra* note 2.

300. BIOTECH 96, *supra* note 2, at 10; *see, e.g.*, Ronald Rosenberg, *Genzyme IPO Scores*, BOSTON GLOBE, Oct. 14, 1995, at 64 (Company provided one of the highest stock offerings of the year due to anticipated FDA approval of its two surgical coating products.).

have been engaged in R&D for more than a decade, have no products in commerce.[301] The length of the FDA approval process affects the companies whose products are being reviewed directly and also may affect the market-wide impression of the industry.[302] One high-profile genotech company's failure can have an industry-wide impact and there have been many such failures.[303] Accordingly, one of the most pressing concerns of CEOs of genotech companies is the ability to get technologies through the FDA and to market, which, in turn, affects their most pressing concern—financing.[304]

The difficulty the FDA has in evaluating these new genotechnologies is illustrated clearly by the example of its review of dexfenfluramine, an obesity drug developed by Interneuron Pharmaceuticals Inc. On September 28, 1995, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee ruled

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301. McDermott, *supra* note 7, at A1. Robert E. Ivy, Chairman, President, and CEO, RIBI Immunochem Research, Inc., *quoted in* BIOTECH 95, *supra* note 2 at 26 ("If you are in the pharmaceutical business, your first client is the FDA. After satisfying the FDA, your client is the patient. After you satisfy the patient, you can start paying back the shareholder.").

302. Tom Petruno, *Renewed Interest in Biotech Stocks*, CHIC. SUN-TIMES, Jan. 12, 1993, at 40. In the summer of 1995, the Health Industry Manufacturers Association (HHA) released a 275-page study showing that although the number of applications for products has declined, the time it takes to evaluate these applications has increased 1.5 times. *Regulatory Burdens Cited as Leading Cause of Delayed Technology*, HOME HEALTH CARE DEALER/SUPPLIER, July/Aug. 1995, at 20. Ronald Rosenberg, *FDA Panel to Deal with Antiobesity Drug on Monday*, BOSTON GLOBE, Sept. 30, 1995, at 61 (stating that the FDA advisory panel, after an intense nine-hour session, still could not reach a quorum on a fat-fighting drug, and that the company's stock fell as investors tried to gauge the FDA panel's actions).

303. *See* BIOTECH 96, *supra* note 2, at 25-27; *see also* Cassidy, *supra* note 88, at A13-14 ("Demand has crashed because very few venture capitalists are willing to back start-ups after a year in which there were several glaring examples of experimental drugs failing to live up to expectations, companies grappling with long-term financial issues and the growing realization that production costs are often too high for small biotech businesses."); *see also* Day, *supra* note 90, at 18 ("Expectations that the FDA would approve [Medimmune Inc.'s cystic fibrosis] drug had run the company's stock up to more than $36 a share in November 1993. It went crashing down to the $3 to $4-a-share range, stunning company executives."); Kaufman, *supra* note 294, at 1D ("The failure of many biopharmaceuticals in late-stage FDA clinical trials—about 30 in the last three years—has also forced them to confront the staggering cost of financing a biotechnology company."); Ronald Rosenberg, *Biogen Lost a Drug, Kept its Health, Reputation*, BOSTON GLOBE, Nov. 20, 1994, at A1-A2 (providing Biogen as an example of an industry roller coaster trend of companies taking large risks and facing tough declines on research of a single drug that does not produce anticipated results); Rosenberg, *supra* note 87, at 61 (tracking the successful rise in Biogen, Inc.'s stock price with positive test results on an intramuscular drug, Beta Interferon, to treat multiple sclerosis, and susequent plunge with disappointing results on the development of a blood thinner alternative, Hirulog). *Compare* Marc Monseau, *Possible Drug Approval by FDA Helps Boost Shares of Biogen*, BOSTON GLOBE, Mar. 29, 1995, at 31 (reporting a 7.1 % gain in Biogen, Inc. shares due to investor hope that the company would apply soon for marketing approval for its multiple sclerosis product); Ronald Rosenberg, *Optimism Over Antiscarring Drug Boosts Genzyme Shares*, BOSTON GLOBE, Jan. 26, 1995, at 58 (reporting that Genzyme stock climbed more than four points within 30 minutes of the announcement of success with HAL-F, an antiscarring drug which would have a major impact on the market for surgical adhesions).

304. Specifically, the lack of clarity in FDA review standard guidelines concerns these companies. *See* BIOTECH 95, *supra* note 2, at 26.

that dexfenfluramine is effective, but not safe enough for long-term use. When the FDA asked the committee for clarification, an incomplete vote (some panel members had left the room) resulted in a three-to-two vote for approval.[305] Finally, in November 1995, the full panel on a six-to-five vote recommended approval of the drug—the first obesity drug approved by the FDA in twenty years.[306]

Currently, both Congress and the industry are pressuring the FDA to reform the drug-approval process.[307] Critics charge that the FDA has contributed to increasing health care costs, monopolistic practices, unavailability of crucial therapeutics to particular categories of patients, and a decline in the American advantage in biotechnology in the international arena.[308] The congressional reform effort is bipartisan, and it includes hearings being conducted by the Senate's Labor and Human Resources Committee and the House Commerce Committee's subcommittee on Oversight and Investigation.[309] Although no new legislation is expected until 1996, existing legislative proposals include: (1) contracting out product reviews to private testing laboratories to speed up product approvals; (2) eliminating the requirement that the manufacturers of genotechnologies build full-scale manufacturing facilities as a prerequisite for approval of their therapeutics; (3) eliminating required FDA review when a company makes standard changes in its manufacturing practices; and (4) harmonizing FDA regulatory requirements with those of other countries to avoid repetition of clinical efforts.[310] Although the Clinton Administration has announced revisions of FDA rules concerning biotechnology products, legislation is required to codify these regulatory modifications.[311]

Perhaps more significant, in April 1995 the FDA itself identified reforms that could accelerate substantially the drug review process. To supplement proposals two and three outlined above, the FDA proposed that: (1) a two-year

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305. Rosenberg, *supra* note 87, at 61.

306. Joseph Pereira, *FDA Advisory Panel Urges Approval of the First New Diet Pill in Decades*, WALL ST. J., Nov. 17, 1995, at B2; Ronald Rosenberg, *Panel's OK of Diet Drug Lifts Interneuron Stock*, BOSTON GLOBE, Nov. 18, 1995, at 61 (indicating that the full FDA commission is likely to approve it).

307. *See* BIOTECH 96, *supra* note 2, at 36.

308. *Id.*

309. *Id.*

310. *Id.* at 37. Eighty-five percent of genotech CEOs have predicted that such reforms will have a positive impact on the industry. *Id.* at 10. There also is a proposal to provide genotech companies with more flexibility in exporting products that are awaiting FDA approval to foreign industrialized countries. *Id.* at 37. In light of the added caution many other nations have demonstrated towards genotechnology, such legislation could lead to significant political backlash against the United States. *See supra* Section II.B.2.; *infra* Part III.B.2. Accordingly, great attention should be paid to cultural and political differences between the United States and target test markets before such legislation is enacted.

311. Schwartz, *supra* note 271, at A19.

pilot program be created to examine the feasability of private-sector evaluation of some low-risk medical devices; (2) FDA standards be harmonized with international medical standards, enabling the FDA to accept drugs tested abroad rather than mandating retesting in the United States; (3) a single major clinical trial be accepted as evidence that a drug works; and (4) 125 categories of very low-risk medical devices be added to the 440 already exempt from FDA review.[312] In November 1995, the FDA announced that it intends to streamline its approval process for genotech developers by, among other things, eliminating the requirement that the FDA approve manufacturing plants for genotech drugs.[313]

The proposals identified above generally merit serious consideration, and some should be implemented immediately. It seems particularly appropriate to utilize the expertise of the private sector in evaluating genotechnologies, which are novel technologies developed by leaders in science and academia whose expertise is rare and, in some cases, perhaps impossible to match. The FDA's proposal to introduce a two-year pilot program for low-risk technologies is a safe beginning for such reform. Shifting such basic testing to laboratories with some political distance from the drug-approval process may result in accelerated review. Moreover, even if the direct involvement of private laboratories is limited to very low-risk technologies, the overall review process may benefit simply by exposing FDA laboratory workers and administrators to the efficiencies of private sector commercial laboratories. Also, this limited reform may lead to delegation of the basic testing components for certain complex technologies to the private sector.

Expanding the categories for low-risk medical devices would enable the FDA to focus its limited resources on other more complex technologies. Such reform also would benefit the private sector by enabling some genotech companies to begin generating or expanding revenues. However, the impact of this change on the genotech industry is likely to be minimal since most genotech devices are classified as Class III.[314] Furthermore, this proposal raises serious questions. For example, many of the genotech products which fall into the "devices" category are diagnostics. Though such products may pose a minimal physical health risk to patients, the mental and societal risks accompanying such technologies are considerable.[315] As discussed in Section III.D, these issues must be addressed and resolved *before* patient exposure to genotech diagnostics is expanded.

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312. BIOTECH 96, *supra* note 2, at 58.

313. Acron Zitner, *FDA Set to Give Biotech Firms a Boost*, BOSTON GLOBE, Nov. 9, 1995, at 63; *see also* Schwartz, *supra* note 271, at A19.

314. Diane E. Hoffman, *The Biotechnology Revolution and its Regulatory Evolution*, 38 DRAKE L. REV. 471, 511-12 (1988-89).

315. *See infra* notes 419-33 and accompanying text.

Harmonizing FDA regulatory requirements with those of other countries and accepting a single major clinical trial as evidence of a drug's efficacy would avoid wasteful duplication of effort. The world-wide scientific community is particularly accustomed to working together and sharing information in the field of genotechnology as a result of efforts such as HGP and the work of organizations such as HUGO and UNESCO. In fact, as stated earlier, many European-based pharmas have invested in genotechnology developed in the United States, and some United States genotech companies, such as Genzyme, now are conducting clinical trials abroad. If repetition of clinical efforts were avoided, more resources could be allocated to postmarketing surveillance. In fact, regardless of whether such reforms are realized, meaningful post-marketing surveillance *must* be mandated to ensure responsible application of genotechnologies. Long-term surveillance is the only means to evaluate satisfactorily the safety of many genotechnologies, the side effects of which may take years to emerge and are impossible to assess fully at the pre-marketing stage. Moreover, such reform is commercially viable because the expense of post-marketing surveillance would be offset by revenues received by genotech manufacturers marketing the drugs being observed. In other words, costs would be shifted to the post-marketing stage, with earlier commercialization financing this more extensive observation. So long as it is accompanied by adequate safeguards and meaningful consent requirements, such reform also is the responsible regulatory course from the patient perspective. Withholding technologies which extensive clinical trials suggest will have a dramatic impact on the lives of the terminally ill and where existing testing capabilities have been exhausted is simply not an acceptable option.

Improving the drug-approval system for genotech therapeutics and diagnostics would profoundly affect the genotech and health care industries, especially given the number of such technologies now in the drug-approval process.[316] In addition to the proposals mentioned above, another possibility for reform should be considered. Minimizing the "biologics" classification would avoid many of the added regulatory burdens currently imposed, the most onerous being: (1) the requirement that the products used in Phase III trials be produced in the intended commercial-scale manufacturing facility; (2) the limitation of access to marketing licenses to companies that manufacture the biologic; and (3) the mandate that each significant participant in the

316. Such improvement also would, at least to some extent, preempt interference with clinical trials by patients utilizing the "information super highway." It already has been documented that patients suffering from amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, involved in Neurontin (a drug used to treat epilepsy) trials went on-line and reported positive results, enabling each other to determine if they were receiving placebos or the real thing. *See* William M. Bulkeley, *E-Mail Medicine: Untested Treatments, Cures Find Stronghold on On-Line Services; Doctors Fret the Gravely Ill May Share Information and Skew Drug Testing*, WALL ST. J., Feb. 27, 1995, at A1.

manufacturing process hold establishment and product licenses for the new technology.[317] These requirements are anachronistic remnants of a time when biologics could not be produced with the purity of traditional drugs—a time when the science of genetics engendered fear rather than confidence in its practical prospects for improving human health. For the many modern biologics that can be produced with drug-like purity and consistency, these added burdens should be removed.[318] An alternative possibility is simply eliminating the added burdens under the PHS, while maintaining the biologics classification for other purposes, such as post-marketing surveillance, and the minimization of bureaucratic delays. Such reform would, among other things, enable genotech companies to enter manufacturing agreements with pharmas without giving up ownership interests in the technologies, thus reducing some of the dangers regarding pharma investment identified above in Section I.B.

A more ambitious solution would be to develop a new classification system tailored to genotech-based drugs. Such a system would be flexible, with multiple drug-approval tracks and clinical trial alternatives created with patient and economic cost-benefit analyses in mind and building upon the reforms introduced by the FDA in 1988 and by PDFA in 1992. There are already some indications that the FDA and NIH are recognizing this need for added flexibility. For example, as stated above, the FDA is permitting Genzyme to continue its new cartilage restoration procedure pending development of FDA regulation for such therapies, and some self-reforms already have been announced by the FDA.[319]

The potentially conflicting objectives of making new technologies available to patients and protecting the public from possibly harmful technologies are embodied in all drug-approval processes and create a necessary but extremely difficult cost-benefit analysis. The difficulty of such an analysis is directly proportional to the novelty (and uncertainty) of the technologies and their potential to improve human health. The analysis becomes especially challenging when highly experimental technologies offer potential treatment for those who are terminally ill and, more generally, for those who are suffering from conditions not adequately treatable with

317. *See* 21 C.F.R § 601.1-.51 (1995).

318. *See* Gamerman, *supra* note 243. The arguments for eliminating the distinction between the review processes for biologics and more traditional drugs may be summarized as follows: (i) modern biologics can be produced with drug-like purity and consistency; (ii) there are no scientific distinctions between many products regulated as drugs and those regulated as biologics; (iii) there are no significant regulatory controls under Biologics Act that are/could not be implemented under FDCA. *Id.* at 226. In addition, "[b]ecause of the policies and regulations imposed by CBER, biologics developers must commit far more of their limited financial resources to manufacturing before they know whether they have an appropriate product than do drug developers." *Id.* at 214.

319. Telephone Interview with Mark A. Hofer, General Counsel, Genzyme Corp., Nov. 7, 1995; *see* Schwartz, *supra* note 271, at A19.

established technologies. Many current biotech products do not substantially treat their target diseases, and researchers and regulators may have difficulty reaching agreement on how to design effective clinical studies and what the goals of such studies should be.[320]

For treatments targeted to the terminally ill,[321] CBER might adopt an approval track approach more like the United Kingdom's.[322] This approach is designed to (1) allow drug developers to make new technologies available to patients unable to wait; and (2) remove the "experimental" label from these technologies earlier, thereby both removing insurers' justification for refusing coverage and generating patient data more quickly. The resulting economic advantages for drug developers would have to be accompanied by stronger patient consent and care requirements for health care providers and heavier post-marketing requirements on the developers.[323] Such an approach would reflect the novelty of many genotech therapeutics and diagnostics, the long-term side effects and effectiveness of which may not be determined any other way. Additional possibilities include aggressively expanding the use of Treatment INDs,[324] Group C drugs for cancer, and Parallel Drug Tracking for low-risk genotechnologies such as tissue growth and adhesion technologies.[325] Another more prudent possibility is the acceleration of Phase III for potentially life-saving technology by shortening trial time periods and reducing the number of patients required to be tested where the technology is

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320. *See* BIOTECH 95, *supra* note 2, at 26.

321. A change in requirements for terminally ill patients would have to come from the regulators, because the Supreme Court has held that it cannot come from patients or through the courts. *See* United States v. Rutherford, 442 U.S. 544 (1979). In *Rutherford*, the Supreme Court found that the lower court had erred in holding that the FDA *should* apply a looser standard in approving drugs to be used by terminally ill patients on the grounds that such patients are going to die without such drugs. 442 U.S. at 550-551. The Court unanimously held that the FDA has authority to require safety and effectiveness for all drugs, including those to treat the terminally ill, and that Congress intended for the FDA to shield even terminally ill patients from fraudulent cures. 442 U.S. at 558.

322. Drug testing in Great Britain also begins with animal testing, and investigational and experimental drug use on humans requires certification and licensing. However, therapeutic use (physicians administering drugs to patients) is permitted and excluded from the certification requirement. It also is accompanied by reliance on and close patient monitoring by health care providers and stringent post-marketing surveillance requirements on drug developers. Henry, *supra* note 219, at 637.

323. *Id.* at 637-38.

324. "The Treatment IND is intended to speed availability of drugs by allowing a sponsor to distribute a drug more widely than before it has all the data needed to obtain a full market approval under a New Drug Application." *Id.* at 624. Treatment INDs allow companies to charge the patients for the investigational drug, thus permitting patients access to drugs about two to three years earlier. Along with its benefits, such a system leads to a difficult accessibility issue because many insurance companies will not pay for investigational drugs. "Treatment INDs could . . . set up a two-tiered system whereby wealthy patients would obtain the experimental therapy and those who could not afford the therapy would end up in clinical trials. There is also fear that drug developers may price the investigational drugs too high." *Id.* at 625.

325. *See generally id.* at 623-28.

for life-threatening and incurable diseases. Such a reduction in pre-market testing again should be offset by imposing a higher post-marketing requirement.

There are obvious dangers accompanying these proposals. These dangers were illustrated in the recent failure of an NIH-sponsored experimental AZT-based AIDS vaccine, which was administered to at-risk newborns and to infected expectant mothers to impede transmission of the AIDS virus from mother to child.[326] Noteworthy genotech disasters include those experienced in trials by Xoma Corp. and Chiron, which had a profound negative impact on the industry and its innovation.[327] Recently, an experimental drug was tested on seventeen advanced cancer patients by Genetics Institute. In early test-tube experiments, the drug restored normal immune responses in cells that were damaged by the AIDS virus. However, a Phase II trial of the drug resulted in the death of one patient and the hospitalization of eleven others.[328]

The general dangers of administering highly experimental protocols are well documented,[329] as are the lawsuits which arise out of them,[330] the impact of failures on the value of developers' stock,[331] and the lack of a

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326. "AZT, the most common antiviral drug used against the AIDS virus, has been dropped from a clinical trial among children after it proved to be the least effective, and to cause the *highest rate of side effects* of three treatments, the National Institutes of Health announced yesterday." *AZT is Dropped from Clinical Trial*, BOSTON GLOBE, Feb. 14, 1995, at 6 (emphasis added).

327. *See* Benedict Bahner, *Hanging Back: Biotechnology Companies Are Struggling to Survive at a Time of Investor Reluctance*, CHEM. MARKETING REP., Mar. 7, 1994, at 10 (Depressed stock prices are due in part to "the failure of high-profile septic shock therapies from Centocor, Xoma and Synergen . . . . Most notable was Centocor's HA-1A/Centoxin, whose clinical trials ended when tests showed a mortality rate 'excess' among patients tested with it."); *see also The "Virtual" Pharmaceutical Company and Other Trends in Strategic Alliances*, PRESSWIRE, Jan. 24, 1995 (discontinuation of clinical trials of Chiron drug for septic shock had a minimal impact on the company's stock price "compared with a 50% fall in capital value" of Centocor, Synergen and Xoma which had "product failures in the same therapeutic areas").

328. Mitchell Zuckoff, *Drug Inquiry Targets Absence of Use of Test Dose, Waiting Period*, BOSTON GLOBE, June 15, 1995, at 51; *see also Genetics Institute Hopes to Restart Drug's Testing*, BOSTON GLOBE, July 23, 1995, at 74 (releasing preliminary results of internal investigation).

329. *See generally* David W. Bates et al., *Incidence of Adverse Drug Events and Potential Adverse Drug Events: Implications for Prevention*, 274 JAMA 29, 29-35 (1995). These dangers have been made evident in recent investigation of mistakes regarding experimental cancer treatments administered at the Dana Farber Cancer Institute. *See* Richard A. Knox & Daniel Golden, *Drug Dosage Was Questioned*, BOSTON GLOBE, June 19, 1995, at 1, 20; Richard Saltus, *The Doses and Risks of Chemotherapy*, BOSTON GLOBE, Mar. 27, 1995, at 37 (Experimental chemotherapy treatments are "a game played very close to the edge."). *See also* Scott Allen, *Deadly Legacy*, BOSTON GLOBE, May 29, 1995, at 27-28 (emphasizing that experimental cancer treatments carried out in the 1950s and 1960s are now generating law suits); Day, *supra* note 90, at 18 (noting that failed tests are one of the genotech industry's "major challenges.").

330. *See, e.g.*, Allen, *supra* note 329, at 27-28.

331. *See* Day, *supra* note 90; Rosenberg, *supra* note 87, at A1 (noting that abandonment of one drug's development after disappointing test results caused Biogen's stock price to drop 25% in a few days); *U.S. Bioscience Stock Falls 69%*, BOSTON GLOBE, Dec. 18, 1994, at 60 (noting steep fall in stock price following failure to win FDA approval for experimental cancer drug,

systematic mechanism for reporting mistakes regarding experimental treatments.[332] Nevertheless, the danger of suffering or dying from a terminal illness while a viable treatment remains in the existing drug-approval process—and therefore unavailable—also is obvious, as is the danger of suffocating economically an industry capable of generating a myriad of such technologies.

The changes discussed above would result in a shift of the genotech industry's development costs to the post-marketing period, when patients are using and paying for their technologies.[333] From the patient's perspective, additional risk would be assumed in exhange for quicker access and, for the terminally ill, a chance for extended life.[334] Along with the heavier post-marketing requirements discussed above, Congress should enact a meaningful informed-consent requirement accompanied by a regulatory compliance defense. This enactment would both enhance patient voluntariness and understanding and limit drug developer liability for unanticipated and unforeseeable effects, which would have to be carefully and explicitly defined.[335] Such legislation should include a mandatory counseling component. True informed consent may not be realized through standardized forms and/or from the apparent assent of the extremely vulnerable terminally ill. Essentially, these proposals would form a more responsible legal and regulatory infrastructure for the commercialization of genotechnologies, and increase the likelihood that delays in their availability would reflect responsive public policymaking rather than regulatory nonresponsiveness or an inability to grapple with the issues raised by these new technologies.

Ethyol).

332. *See* Richard A. Know & Brian C. Mooney, *Hospital Dosage Mistakes Not Rare*, BOSTON GLOBE, Apr. 16, 1995, at 1, 14.

333. An overview of arguments for shifting clinical data requirements to post-marketing is provided in Henry, *supra* note 219, at 624, 638.

334. Pulmozyme, the genetics therapeutic for cystic fibrosis discussed *supra* note 274, was approved by European regulators in 1993. *See* Louis Trager, *Europe OKs New Drug by Genentech; Cystic Fibrosis Treatment Should Benefit Patients*, S.F. EXAM., Dec. 17, 1993.

335. See Margaret Gilhooley, *Innovative Drugs, Products Liability, Regulatory Compliance, and Patient Choice*, 24 SETON HALL L. REV. 1481 (1994) for a discussion of the importance of patient-care safeguards and consent requirements in light of the inherent patient/subject conflict involved in treating patients on experimental protocols. Safeguards cannot completely eliminate the possibility of delayed effects during trials and even once technologies have been marketed, especially for genuinely novel technologies. *See id.* at 1482. A regulatory compliance defense could serve to limit legal liability for this inevitable occurrence, thereby encouraging innovation. Such a defense as proposed by one commentator should be accompanied by supplementing drug labeling with a digest of current literature on scientific studies relating to the drug that would be accessible to both doctors and patients. *Id.* at 1482-88. An informed consent requirement with a counseling component should also accompany such a defense.

B. *Property Rights and Other Market Protections*

The novelty of genotechnology and the relative lack of jurisprudence applying traditional patent policy to it have encouraged genotech firms to "hedge their bets" by filing patent applications. For example, despite the PTO's denial of the NIH's patent applications, companies continue to apply for patents on partial gene sequences.[336] This trend could result in several companies each obtaining a patent on a segment of a complete gene,[337] thereby necessitating elaborate licensing arrangements to enable any one of these companies to commercialize the entire gene or its products.[338] Issues of patent ownership and validity are becoming more critical as technologies become commercially viable and companies increasingly devote resources to enforcing their patents through the courts.[339]

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336. Smith & Kettelberger, *supra* note 151, at 49-50, 57 (noting that more than a dozen companies, including Incyte Pharmaceuticals, are vying to sequence DNA fragments, but since patent applications are secret, there is no available estimate of how many patent applications claim partial DNA sequences); *see also* Carey, *supra* note 8, at 74 (noting that HGS was "madly filing" patents on gene fragments). The company filing the most gene sequence patents is TIGR, headed by J. Craig Venter and affiliated with HGS whose CEO is Dr. William A. Haseltine. *See supra* note 100 and accompanying text. Recently, as Venter has turned to more basic science and Haseltine has duplicated Venter's sequencing and begun producing 750,000 DNA code pieces daily, the relationship between TIGR and HGS has become strained. Carey, *supra* note 8, at 77. Venter's arrangement with HGS gave him the right to publish his findings in return for HGS receiving commercial rights to the genes he discovered. *Id.* To ensure its commercial advantage, and perhaps also to prevent any patent it applies for from being denied on the ground of obviousness, HGS would now like Venter to delay publication. *Id. See also* 35 U.S.C. § 103 (1988 & Supp. V 1993) (obviousness bar to patentability). Merck is attempting to counter HGS's efforts, however, by making gene fragments publicly available. Carey, *supra* note 8 at 73. "Merck executives figure that if everyone has the same information, the company's vaunted research and development department can win most of the races to market. 'Making drugs from genes is like going from a dictionary to the works of Shakespeare,' explains Merck's Alan R. Williamson, vice-preseident for research strategy worldwide." *Id. See also* Elvyse Tanouye, *SmithKline Beecham Leads in Race to Use Genetics to Find Drugs*, WALL ST. J., Nov. 24, 1995, at A1, A5 (detailing Merck's plans to deposit all results from its work with Washington University in the federal government's gene databank which is accessible via the Internet to any scientist and illustrating how such databanks can be searched for the genetic foundation of a new drug which can then be used to create a competing product).

337. Smith & Kettelberger, *supra* note 151, at 47.

338. *Id.* The transaction costs of commercialization under such circumstances would likely be considerable. If licensing were to become a pervasive problem for the industry, an industry group might form—like ASCAP or BMI—to centralize licensing and decrease transaction costs.

339. *See* Day, *supra* note 90, at 18 (noting that many companies devote considerable resources to launching or defending against patent suits); Eric C. Woglom & Margaret A. Pierri, *U.S. Is Unifying Utility Requirements*, NAT'L L. J., Feb. 20, 1995, at C37 (focus of patent activity in genotech moving from procurement to enforcement); *Amgen Wins Round in Patent Dispute*, L.A. TIMES, Feb. 15, 1995, at D2 (federal district court upheld decision finding Genetics Institute's patent for Epogen invalid and unenforceable against Amtech); Sally Lehrman, *Genentech, Lilly Settle 8-Year Fight Over Drug*, S.F. EXAM., Jan. 6, 1995, at B1 (noting that Eli Lilly settled patent suit over Genentech's human growth hormone for $145 million, and that companies spent $75 million protecting respective technologies).

Because of the complex funding structure of most research efforts—with money provided by government, academia and industry—ownership of the resulting work product and any patent rights thereto may be unclear.[340] An example is the controversy over the BRCA1 gene, mutations of which have been found to cause a predisposition to breast and/or ovarian cancer.[341] The work isolating the gene was conducted in collaboration by researchers at the NIH, the University of Utah Medical Center, McGill University, Eli Lilly, and Myriad Genetics, Inc.[342] However, the patent application named only researchers from the University of Utah and Myriad Genetics as inventors.[343] The NIH, which had provided valuable assistance to the project at taxpayer expense, objected.[344] Eventually a settlement was negotiated resolving control of diagnostic testing and treatments, and the NIH was added to the patent.[345] These types of disputes are likely to continue to arise as research funded by government agencies, academia and the private sector results in commercialized technologies.

With pharmas expressing greater interest in genotech companies and their technologies, and with financial stakes rising as commercialization of genotechnology begins, the validity of patents is likely to be challenged more often.[346] The PTO's new utility guidelines[347] and recent issuance of some

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340. *See supra* Section I.B for a discussion of collaborations involving government, academia and industry.

341. Malcolm Skolnick et al., *The BRCA1 Gene: Commercialization vs. the Public Interest*, HEALTH L. NEWS, Mar. 1995, at 2 ("The BRCA1 is likely responsible for approximately half the incidence of hereditary breast cancer or about five percent of all breast cancer diagnoses."); *see also* Richard Saltus, *Gene in Some Jewish Women Tied to Cancer Risk*, BOSTON GLOBE, Sept. 29, 1995, at 1 (stating that 1 in 100 women of European Jewish heritage may carry BRCA1, a higher rate than that found among non-Jews); Richard Saltus, *Genetic Afflictions Evolved from Ashkenazi History*, BOSTON GLOBE, Sept. 29, 1995, at 7.

342. Skolnick et al., *supra* note 341, at 2.

343. *Id.*

344. *Id.* ("Rep. Wyden [D-Ore.] noted that NIH had provided valuable and seminal assistance to the project and that since the government had a role in the discovery and the research had been partly financed by the taxpayers it was important for NIH to insure that BRCA1 would be used for the public good and fairly priced."). This objection seems somewhat anomalous in light of general federal technology transfer policy described in Section II.B.1.

345. *Id.* Under the agreement, two NIH scientists responsible for the background research are to be listed as co-inventors on the patent application and NIH will receive 25% of future royalties. Anne Wilson, *U., Parties Settle Dispute on Cancer-Gene Patent*, SALT LAKE TRIB., Feb. 16, 1995, at B1.

346. *See, e.g.*, Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200 (Fed. Cir. 1991) (addressing defendant's counterclaim that Amgen's patent was invalid). A duly issued United States patent carries with it a presumption of validity that must be rebutted by the alleged infringer. 35 U.S.C. § 282 (1988 & Supp. V 1993).

347. For the last several years, companies complained that the PTO had been holding genotech inventions to higher standards of utility and non-obviousness than other, more traditional inventions. *See* Woglom & Pierri, *supra* note 339, at C37, C38 (PTO established special section—"Group 1800"—to evaluate genotech patents; as time passed, patent bar began to believe that genotech applications were held to a higher standard of utility than that applied in other

patents of questionable validity make this likely. For example, in March 1995, the PTO granted a patent to Dr. W. French Anderson and the NIH which covers "any method of introducing genetically altered human cells into a patient to combat disease."[348] The NIH has granted Genetic Therapy, Inc. an exclusive license to commercialize the underlying technology.[349] Although the patent has been derided as overbroad,[350] it may be cheaper for other companies to license the technology than to litigate the validity of the patent.

This controversy highlights an important policy concern: to the extent that the PTO has de facto relaxed its requirements for genotech inventions and will issue more questionable patents,[351] the rest of the industry bears the burden of either litigating the validity of these patents or entering into license agreements with those who hold them. Assuming many genotech companies opt for the latter, probably cheaper, alternative, then the PTO essentially has facilitated a redistribution of wealth within the industry by granting those allotted questionable patents something of value without the public receiving comparable value in the form of the information disclosed in the patent specification. This result is at odds with the traditional view of patents as a quid pro quo for disclosure of information meeting the rigorous statutory standards.

Simply stated, while the United States, through the NIH, may have "jump started" the genotech industry by encouraging early patenting of discoveries, it has succeeded primarily in sowing confusion and litigation. These controversies demonstrate that the PTO's application of statutory standards in the context of genotechnology should be scrutinized for consistency with traditional applications of those standards and the fundamental objectives of the patent system to ensure that the policy objectives underlying those standards are not lost.

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examining groups; length and difficulty of genotech patent prosecution supported this claim; PTO accused of functioning like second FDA). The PTO responded with new guidelines that should make it easier for genotech firms to obtain patents. *Id. See also Utility Examination Guidelines and Legal Analysis Are Finalized*, 50 PAT. TRADEMARK & COPYRIGHT J. (BNA) 281 (1995). Note that the guidelines addressed only the § 101 utility requirement, and did not clarify the standards for non-obviousness.

348. Slind-Flor, *supra* note 186, at A6..

349. *Genetic Therapy, Inc. Announces Issuance of Broad Gene Therapy Patent*, Business Wire, Mar. 21, 1995, *available in* WESTLAW, Newswires & News Services, Business Newswires, Business Wire File (license granted under CRADA between NIH and GTI).

350. *Id.*

351. *See* John H. Barton, *Patent Scope in Biotechnology*, 26 INT'L REV. INDUS. PROP. & COPYRIGHT L. 605 (1995) (arguing that broad patents may hamper innovation and suggesting legal reforms); *cf. Patents: Utility Examination Guidelines and Legal Analysis Are Finalized*, 1995 DAILY REPORT FOR EXECUTIVES (BNA) 141 (1995) (reporting PTO publication of final guidelines for review of liberalized patent application requirements).

1. *The Basics of Patent Policy*

At the heart of all patent systems is the theory that if society "honor[s] the creator of a useful thing, . . . society will get more useful things."[352] This formulation represents policy judgments based on both economics and ideas of social welfare that are reflected in the substantive provisions of the Patent Act.[353] Economically, the patent system is a response to a "public goods" problem:

> In economic terms, a "public good" is one that has the property of nonexclusivity: Once the good has been produced, it is impossible (or prohibitively costly) to exclude any individual from benefiting from it, whether or not he or she pays. . . . In granting a limited monopoly through copyright or patent, government attempts to compensate for distortions arising from nonexclusivity. According to this rationale, without the counterbalancing grants of monopoly power bestowed through copyright and patent, the inability of authors and inventors to appropriate economic returns from their labors would result in the underproduction of new works and inventions.[354]

Through amelioration of the public goods problem, the patent system aims to provide incentives for research and development.

By granting a limited monopoly, the patent system not only spurs development but also introduces market imperfections.[355] Particular provisions of the Patent Act help ensure that the detriments associated with monopolies do not outweigh the benefit of increased investment in inventive

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352. MERGES, *supra* note 192, at 2 (noting also that the textual statement embodies the tension that permeates all patent debates—tension inherent in a system in which social benefits in the form of technological progress are achieved through private rewards).

353. 35 U.S.C. (1988 & Supp. V 1993). Congress' power to enact statutes like the Patent Act is granted by the U.S. Constitution in art. I, § 8, cl.8: "The Congress shall have the power . . . to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries . . . ." *See* U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, FINDING A BALANCE: COMPUTER SOFTWARE, INTELLECTUAL PROPERTY AND THE CHALLENGE OF TECHNOLOGICAL CHANGE 185 (1992).

354. U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, *supra* note 353, at 185. Note also that market imperfections created by the public goods problem may be corrected by government subsidization. In the genotech area, government has used not only the grant of exclusive rights through the Patent Act to help encourage genotech innovation, but also has been a primary source of funding for that activity. *See supra* text accompanying notes 155-160, 190-94.

355. U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, *supra* note 353, at 186 (monopolists will tend to produce less of the good and charge a higher price; a monopoly can create excessive incentives for innovative activities accorded monopoly status; a monopoly can produce "spillover" effects—externalities—in other markets; administration of intellectual property regime is costly).

activities. For example, exclusive patent rights[356] are limited temporally,[357] as well as subject to certain other limiting doctrines.[358] Moreover, an inventor will not qualify for a patent in the first instance unless his or her invention meets the statutory requirements of novelty, utility and non-obviousness and is adequately described in an enabling disclosure.[359] Thus, in return for the grant of a limited statutory monopoly, the patentee must agree to disclose his invention.[360] These limits help to correct the market imperfections of a monopoly.

The Patent Act aims to increase the store of useful information available to society and other inventors by granting exclusive rights to encourage inventors to invest in those activities likely to produce such information. At first glance, the theoretical underpinnings of the Patent Act seem to support fully granting patents on genotech inventions.[361] The genotech industry generates a wide spectrum of technologies. Furthermore, the investment in bringing a new genotech drug to market is usually large—as much as $400 million—while the time lag between idea and introduction of the drug to market may be as long as twelve years.[362] Because investor mentality tends to be "if you cannot patent it, do not invest in it," without some type of exclusive rights to enable firms to recoup their investments in genotech

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356. 35 U.S.C. § 154 (1988 & Supp. V 1993) ("Every patent shall contain . . . a grant to the patentee . . . of the right to exclude others from making, using, or selling the invention throughout the United States . . . .").

357. Woglom & Pierri, *supra* note 339, at C37, C39 (in 1995, Congress changed the term of a patent from 17 years from date of issue to 20 years from date of filing so as to conform to GATT specifications).

358. For example, the judicial doctrine of patent misuse—closely related to antitrust law—prevents the patentee from leveraging his monopoly in one market into another. *See generally* MERGES, *supra* note 192, at 866-928; U.S. CONGRESS OFFICE OF TECHNOLOGY ASSESSMENT, NEW DEVELOPMENTS IN BIOTECHNOLOGY: PATENTING LIFE 58 (1989) (limited experimental or fair use exceptions may protect otherwise infringing uses).

359. 35 U.S.C. §§ 101-103, 112 (1988 & Supp. V 1993).

360. The intended benefit to society has shifted over time:

> Under the original patent systems, society's benefit was the introduction of a new art or technology into the country. By the late eighteenth century, the primary benefit was seen as the technological know-how behind the inventor's patent. The beneficiaries on this view were not just the public at large, but instead others skilled in the technical arts who could learn something from the patentee's invention. This was a major change in the economic role of patents, for it shifted the emphasis from the introduction of finished products into commerce to the introduction of new and useful information to the technical arts.

MERGES, *supra* note 192, at 5-6.

361. Woglom & Pierri, *supra* note 339, at C37-38 ("Patents are the lifeblood of the biotechnology industry—an industry that offers much promise, but as of yet limited profits. As capital-raising tools, patents are critical to the industry's staggering research and development efforts.").

362. *See supra* note 239 and accompanying text.

advances, research may never be conducted at all or, if conducted, may never move out of laboratories and into the marketplace.[363]

2. *The Patent Act and Genotechnology*

Pursuant to section 101 of the Patent Act, "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[364] Thus, for an invention to qualify for patent protection, it must fall within the categories of statutory subject matter and be both novel and useful.[365] Additionally, under section 103 of the Act, the invention must have been non-obvious to a person of ordinary skill in the art at the time the invention was made.[366] Finally, to obtain a patent, the applicant must provide a written specification that sets forth an enabling disclosure.[367]

Since *Diamond v. Chakrabarty*, it has been settled law that, while naturally occurring phenomena are not patentable, genetically *engineered* living organisms may fall within the Patent Act's statutory subject matter.[368] *Chakrabarty* reiterates the historic substantive distinction between discovery and invention. Discovery of a naturally occurring phenomenon, despite the fact that it may require a large investment, is not patentable while invention—human-engineered transformations of natural substances—may be.[369] Thus, pursuant to existing PTO policy and established law, patent protection applies to "those organisms that an inventor has altered in a new

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363. Victoria Slind-Flor, *Biotech Bar Frets About the Future*, NAT'L L. J., June 5, 1995, at A6 (reporting that the Biotech Industry Organization, responding to opposition of the religous right, stated that without patent protection, the "next generation of modern medicines and cures will never get out of research labs").

364. 35 U.S.C. § 101 (1988 & Supp. V 1993).

365. In re Bergy, 596 F.2d 952, 960 (C.C.P.A. 1979). Section 102 further elaborates the conditions relating to novelty. *See* 35 U.S.C § 102 (1998 & Supp.V 1993).

366. 35 U.S.C. § 103 (1988 & Supp. V 1993).

367. 35 U.S.C. § 112 (1988 & Supp. V 1993).

368. 447 U.S. 303, 308-10 (1980). The Court upheld a patent on human-made, genetically engineered bacteria capable of breaking down crude oil, concluding:

> The laws of nature, physical phenomena, and abstract ideas have been held not patentable . . . . [Respondent's] claim is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture . . . . [G]enetic technology was unforeseen when Congress enacted § 101. . . . The grant or denial of patents on micro-organisms is not likely to put an end to genetic research or to its attendant risks. . . . Whether respondent's claims are patentable may determine whether research efforts are accelerated by the hope of reward or slowed by want of incentives, but that is all.

447 U.S. at 309, 314, 317.

369. MERGES, *supra* note 192, at 124 (comparing *Chakrabarty* with Funk Bros. Seed Co. v. Kalo Innoculant Co., 333 U.S. 127 (1948)).

and useful way or to genes when they have been isolated as synthetic molecules, *a form in which they do not occur in nature.*"[370] Recently, patents of purified chemicals, including purified genetic sequences, have been upheld as these purified chemicals do not occur in nature.[371]

Less certain is whether patent protection will be available for the discovery of a gene sequence or partial sequence.[372] NIH's patent applications for partial gene sequences generated a well-publicized controversy. The PTO rejected the applications based upon lack of utility, novelty and nonobviousness—not for lack of statutory subject matter.[373] The PTO's action could reflect its desire to avoid the issue of statutory subject matter in this context or a substantiation of the contention that the historical distinction between discovery and invention has been eroded to a nullity.

An applicant for a patent must set forth an invention that is useful, novel, nonobvious, and disclosed in an enabling disclosure in addition to claiming statutory subject matter.[374] Although the PTO's new utility guidelines make it less likely that applications claiming a genotech invention will be rejected for lack of utility, this requirement still presents a meaningful hurdle for the patenting of gene sequences of unknown function.[375] As other governments and companies like Merck publish their genetics findings, particularly with respect to partial DNA sequences, the patenting of later full-length sequences potentially could be barred because they are no longer either novel or nonobvious. Finally, because genotech advances may be difficult to describe in an enabling disclosure, patentees may find it infeasible to provide the specification required by the statute.[376]

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370. Oman, *supra* note 13, at C43 (emphasis added).

371. *See, e.g.*, In re Bergstrom, 427 F.2d 1394 (C.C.P.A. 1970) (holding vasodilators patentable because purified version exhibited properties not possessed by unpurified version). Two commentators have put the point thus:

> Man's act of purifying and isolating a natural substance from its source, and providing the "substantially purified" substance for commercial use has routinely been found sufficient to remove the "phenomenon of nature" rejection from claims to DNA sequences. "The PTO has issued numerous patents on DNA sequences and some of the patents have been judicially enforced, although no one has challenged their validity on the ground that they claim a phenomenon of nature." Thus, such grounds for invalidation seem unlikely.

Smith & Kettleberger, *supra* note 151, at 57 (quoting Rebecca S. Eisenberg, *Genes, Patents and Product Development*, 257 SCIENCE 903, 905 (1992)).

372. *Id.*

373. *Id.*

374. *See* 35 U.S.C. §§ 101-103, 112 (1988 & Supp. V 1993).

375. *See supra* note 347 and accompanying text.

376. *See supra* note 217 and accompanying text (new legislation making it easier for biotech firms to obtain process patents adopted in part to account for difficulties of describing advance in enabling disclosure).

3. *Proposals for Change*

Genotechnology offers perhaps unprecedented potential for the alleviation of human suffering. However, private corporations are unlikely to make the investment required to develop the industry unless they are able to realize a competitive return on that investment. Uncertainty often creates risk which causes investors in truly novel ventures to demand a premium on their returns relative to other, safer investments. While there are many factors contributing to the inherent riskiness of a genotech investment, uncertainty regarding patentability is likely to be one of them. Thus, any proposal for change in the patent system should at least attempt to make the patentability of genotech discoveries and the enforcement of resulting patents more predictable.

First, the law should be clarified by a return to the first principles enunciated in *Chakrabarty*.[377] Mere "discoveries" of partial or full gene sequences and/or the proteins a gene produces (however great these accomplishments may appear today) are just that—discoveries, and not patentable inventions.[378] While this distinction between discoveries and patentable inventions has been ignored in recent years, it should be revived. A patent is not a reward for effort or money expended in discovering nature but, rather, a reward for the new and useful invention that results from that discovery. Industry likely will object to this proposal, contending: (1) that substantial investment is required to isolate genes and the proteins they help form and, without patent protection, such advances will not occur; (2) without patent protection, firms will turn to trade secret protection, withdrawing knowledge from the public domain; and (3) the patent system avoids wasteful duplication of research through its disclosure system.[379]

While genotechnology exhibits some characteristics of public goods, the necessary answer is not that all of the industry's R&D must be patentable.[380] Enacting the proposals set forth in Section III.A would alleviate some of the front-loading of costs, lessening the need for strong property rights at the outset. Also, Congress could consider enacting legislation along the lines of the Orphan Drug Act, which would grant more limited exclusive rights to those

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377. *See supra* note 368.

378. *See, e.g.*, Stephen Crespi, *Biotechnology Patenting: The Wicked Animal Must Defend Itself*, 9 EUR. INTELL. PROP. REV. 431, 432 (Sept. 1995) (citing London *Times* commentary on death of EC's draft directive on the Legal Protection of Biotechnological Inventions: "Genes are neither products nor inventions: they are the means by which living things instruct these cells to produce proteins. The isolation of a new gene ought properly to be regarded as an act of discovery—which is not patentable—rather than an act of invention—which is."). Crespi, however, does contend that genes may be patented under certain circumstances. *Id.* at 441.

379. *See* Oman, *supra* note 13, at C43.

380. *See generally* ROBERT COOTER & THOMAS ULEN, LAW AND ECONOMICS, 47-48 (1988) (granting exclusive rights is not only means to solve public goods problem; government could produce the good or grant subsidies for its production).

technologies which are not traditionally considered patentable but for which some market incentives may be required.

Additionally, duplication of effort is already occurring.[381] The most obvious example is the competition between Merck and HGS to identify gene sequences. Merck makes its discoveries publicly accessible while HGS, with patent applications in hand, is charging the private sector a hefty fee for that information.[382] The proposed cabinet-level Science Department,[383] introduced to coordinate R&D programs among federal agencies, may eliminate some of this duplication of effort. Vigorous enforcement of the antitrust laws, particularly those related to monopolies, should also assist in making sure that genetics information remains available even if the consolidation trend in the genotech industry continues.[384]

Besides returning to foundation principles, the PTO should concentrate on (1) ensuring that it applies the correct standard for determining nonobviousness;[385] and (2) expanding and ordering its prior art database so that it does not issue patents that will later be held invalid.[386] The former

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381. *See supra* note 336 and accompanying text. HGP, Merck and HGS efforts are all largely directed to identifying and cataloguing gene sequences. Note that considering this duplication of effort, if patents were to issue on partial gene sequences, (1) the number of interference proceedings would likely increase and (2) complex cross licensing arrangements may have to be concluded. *See supra* notes 337-39 and accompanying text. A bright-line rule may allow industry to devote more resources to drug development by obviating the need for costly patent litigation or incurring transaction costs in licensing arrangements. Moreover, granting patents would hardly avoid duplication of effort as other inventors not licensed under the patent would have to "invent around" it, likely duplicating much of the original patentee's efforts.

382. *See* Tanouye, *supra* note 102, at B1, B5 (Merck making results of its efforts publicly available; HGS does open parts of database to academic and government researchers but keeps other parts private and reserved for commercial use). Incidentally, Merck's approach undercuts the argument that companies will necessarily seek trade secret protection.

383. Browning, *supra* note 179, at 1005.

384. *See* Elisabeth O. Teisberg et al., *Making Competition in Health Care Work*, HARV. BUS. REV., July-Aug. 1994, at 131, 140. Firms like HGS charge a high fee for database access and require that licensees afford HGS a right of first refusal on commercial development. *Survey*, *supra* note 2, at S12 (calling HGS strategy an attempt to corner gene market). However, the antitrust laws were set up to deal with situations in which a company engages in unfair trade practices in furtherance of a monopoly or attempt to monopolize. Moreover, HGS is hardly the only source of genetic information. Merck and HGP plan to make information generally available. This suggests that government and industry should adjust their thinking and focus not so much on patents for gene sequences but on finding a meaningful way to provide access to genetic information, perhaps through an on-line service, using contractual terms rather than patent protection to appropriate any access fee required to recoup investment. *See also* Tanouye, *supra* note 102.

385. *See Patents: Biotech Industry Critical of PTO Examining Procudures at Hearing* 1994 DAILY REPORT FOR EXECUTIVES (BNA) 202 (1994) (many accused PTO of applying stricter standard of nonobviousness for biotech patents than other inventions).

386. *Cf.* John Carey, *Untangling the Legal Strands of DNA*, BUS. WK., May 22, 1995, at 78 (if pieces of genes happen to be in public database, PTO may consider them "prior art" making the full gene unpatentable; if genes become too easy to find and sequence, courts may deem information "obvious" and thus unpatentable).

may require the PTO to establish guidelines much as it did in clarifying the utility standard. The latter may necessitate assistance from industry in formulating a reliable prior art database. Further, Congress should adopt some version of H.R. 1732 to afford third parties more meaningful access to patent reexamination proceedings, helping to assure that issued patents are, in fact, valid.[387]

Finally, Congress may want to consider issues of patent ownership as private and public monies become increasingly commingled, the commercial viability of genotech is realized, and the controversy surrounding BRCA1 is repeated and multiplied.[388] Only the private sector will efficiently, aggressively, and extensively derive practical applications of genotech in the near future, but public concerns regarding the expenditure of federal funds must be addressed. Federal technology policy continues to encourage "giving away" federally funded technology. The revolving door between federal agencies and the private sector continues to spin. Substantial federal funding for genotech research reaches private firms both directly and indirectly through grants to academia. To some extent, the federal approach to technology transfer has been schizophrenic. The federal practice has been to finance research conducted by public institutions which have partnerships with private concerns and to allow these private firms to own the resulting patents and derive revenue therefrom. There is no sign of any deviation from this general approach. However, the approach is undergoing increasing public scrutiny, leading some legislators to question if not the entire federal technology transfer scheme, then at least whether or not the government should be sharing in the revenue derived from the research it funds.[389]

To respond to public criticism, and to allow genotechnology firms more accurately to assess the true costs of their technologies, Congress should consider ways to establish a tangible financial return on its direct investment in genotech which does not remove or impede commercial incentives. For example, Congress should consider requiring the sponsoring agency to include a CRADA provision calling for "royalties" paid into a public fund when a company profitably commercializes technology developed under the CRADA.

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387. *See House Subcommittee Considers Bills on Reexamination and Early Publication*, PAT. TRADEMARK & COPYRIGHT L. DAILY (BNA) 174 (1995) (H.R. 1732 would afford third parties opportunity for greater participation in reexamination proceedings and expand bases for and scope of re-examination).

388. *See supra* notes 341-45 and accompanying text.

389. There is some precedent for the federal government sharing in royalties generated by products based, at least in part, on federally funded research. *See supra* note 345 (describing resolution over patent application for BRCA1); *cf.* Bartlett, *supra* note 184, at C46 (describing NIH regulations published in November 1994 that watch more closely its university and research institutions grant and contract recipients and their involvement with companies for compliance with NIH policies as mandated by the Bayh-Dole Act).

This fund could be used to increase patient access to drug treatments by subsidizing IND Treatments and Group C drugs. The funds also could subsidize the development of effective drugs for rare conditions which otherwise would not be economically feasible to produce. At the very least, these funds could offset cuts in federal funding to teaching hospitals proposed under pending health care reform.

Such an approach should be designed carefully to avoid discouraging firms from entering into CRADAs and partnerships with academia, and from investing in genotech. First, the government should require detailed recordkeeping of its own agencies and the recipients of federal funding to assure that inventors—and thereby patent owners—may be identified with reliability. Second, the royalty cash flow should be structured as a percentage of net profit, in order to ensure that the genotech firms are not forced into incurring losses by paying royalties to the federal government, and, in order to avoid conflicts of interest, channelled into a separate R&D fund to enhance the availability of effective genotechnologies. To protect against commingling the royalty fund with other federal funds, Congress should enact legislation providing for segregation and mandating that a high percentage of the royalties collected in any one year be allocated over the following two years.[390] Disbursements from the fund should be authorized only for certain purposes such as financing genotech treatments for the indigent or offsetting cuts to basic scientific and clinical research funding for teaching hospitals. In this way, private financing may replace some of the federal monies eliminated as the budget is pared.

Of course, administering such a fund may be expensive and, to be effective, would require a level of impartiality seldom demonstrated by Congress. To instill a basic level of meritocracy, the structure could allow all facilities administering genotechnological treatments to apply for grant funding with data demonstrating the efficacy of experimental treatments and budgetary needs on a per patient basis. The grants could be allocated by experts in the field who are capable of both evaluating the applications and avoiding conflicts of interest. In this way, any given experimental treatment would be financed through the institution which demonstrates the greatest capability, perhaps eliminating some duplication of effort and creating incentives for providers to be the best and the first to offer an experimental treatment with proven efficacy. This grant structure is familiar to the science and health care communities. Moreover, the process of preparing such applications may compel institutions to assess their own efficiencies, priorities and capabilities.

390. *See* ROSS PEROT, INTENSIVE CARE: WE MUST SAVE MEDICARE AND MEDICAID NOW 41-48 (1995) (discussing the problem of commingled Medicare funds and the "trust fund" myth). Applicants for a patent are already required to state in the application whether or not the invention was made with federal funds.

C. *Direct Financial Investment and Economic Incentives*

As discussed above, the genotech industry is now consolidating.[391] By itself, this trend is unremarkable and reflects a wider, national trend among industries, including health care.[392] Most industries, as they progress from a scattering of start-up enterprises to a collection of companies with products in their pipelines, go through a phase in which smaller companies combine with larger ones, or go out of business altogether. This consolidation is usually efficient in the sense that economies of scale may be realized while innovation increases, leaving the industry with the appropriate number of firms and capitalization structure to maximize innovation after the shake-out is over. There is ample evidence that genotech stock was overvalued during most of the 1980's, and that analysts either believed the industry's own inflated expectations or failed to understand the inherent risks accompanying the industry's efforts.[393] As these risks became apparent, the downward trend in the prices of stock in genotech companies was inevitable, and it represented nothing more than market adjustment to the true financial and factual situation.[394]

However, as these risks became apparent, investment dollars—particularly from venture capitalists—began drying up, effectively forcing genotech firms into the arms of pharmas.[395] The pharmas are to some extent competitors of genotech firms since genotechnology may supplant the demand for conventional pharma drugs. Thus, while the marriage between genotech companies and pharmas seems necessary and beneficial to the industry,[396] concerns abound. Selling control over genotech therapeutics and diagnostics to the entities that own conventional drugs which will be made obsolete, may delay the introduction of some genotech therapeutics until licenses on the conventional money-makers run out. Pharmas may get more genotech therapeutics and diagnostics to market, but their overhead also may make more

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391. *See supra* Section I.B. However, the massive industry consolidation predicted has not yet occurred. BIOTECH 96, *supra* note 2, at 9. In 1995, "[w]hile 19 companies merged or delisted, an additional 14 went public." *Id.*

392. *See* Teisberg et al., *supra* note 384, at 138; Scot Lehigh, *Caution: Merger Ahead, Unions and Hospitals Are Consolidating—Leading Where?*, BOSTON GLOBE, Aug. 6, 1995, at 71; Robin Sidel, *US Mergers, Led by Media, Banks Break Record in Third Quarter*, BOSTON GLOBE, Oct. 1, 1995, at 55.

393. BURTON G. MALKIEL, A RANDOM WALK DOWN WALL STREET 77-81 (1990) (discussing how analysts, failing to adjust for the vagaries of the FDA approval process, patent uncertainties, and pharma investments, were consistently disappointed in their forecasts of high earnings; genotech stock prices returned to traditional P/E multiples in late 1980s).

394. *Id.*

395. *See supra* Section I.B.2.

396. *Id.*

of them price-prohibitive.[397] This concern is tempered, however, by evidence that market forces are bringing down the cost of drugs overall.[398]

Perhaps most important, increased pharma control may result in a loss of the innovation and entrepreneurial spirit which can be credited with much of what the genotech industry has accomplished to date. According to a recent survey of genotech CEO's, "[f]ifty-four percent of CEOs cited the difficulties of working with the bureaucracy associated with larger companies, and 48 percent noted that hidden agendas can also ruin a deal as, over time, unspoken motives for creating the alliances begin to surface."[399] The more established genotech firms have been able to structure alliances with the pharmas in a manner that allows them to retain some measure of independence.[400] Other smaller firms, however, are less able to do so.[401]

The return of investment appeal of genotech tempers these concerns regarding pharma involvement, lessening the vulnerability of the genotech industry to pharma control. Nevertheless, pharmas already own considerable interests in genotech, and dependency upon pharmas may increase when resources for manufacturing and distribution are needed. Also, widely publicized clinical disappointments and misguided federal policymaking could extinguish easily the present general investment appeal of genotech. Federal policies that slow the commercial availability of technology in a knee-jerk response to clinical disappointments are likely to be much less effective than measures that assess reasonably the risks and benefits involved.

These concerns about pharmas should not necessarily lead to regulation

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397. *Cf.* MALKIEL, *supra* note 393, at 79 (discussing the risk that genotech firms' profits from successful drugs will be siphoned off by marketing partners, usually drug companies).

398. *See generally* THE BOSTON CONSULTING GROUP, INC., *supra* note 12.

399. BIOTECH 95, *supra* note 2, at 36; *see also* Teisberg et al., *supra* note 384, at 138 ("Excessive consolidation will risk creating very powerful [entities] with less need to respond to their customers. It will also limit the experimentation that is critical to stimulating new procedures and treatments."); Burton & Rundle, *supra* note 147 (Eli Lilly selling Hybritech, Inc. which it had hoped would develop monoclonal antibody-based cancer drugs and diagnostic tests; "Former Hybritech executives regard the company's tenure under Lilly as a case study of how a giant pharmaceutical concern can hamstring an entrepeneurial enterprise.").

400. The innovation of these CEOs is reflected in the elaborate alliances they have structured with the academic world to develop their foundation technology and in the even more elaborate alliances they are forming with multinational pharmaceutical companies, not-for-profit organizations, and each other to survive and bring their therapeutics and diagnostics to market. For example, although the genotech CEOs are selling interests in their company's technology to pharmaceutical companies in order to survive, many are entering into "non-monogamous" agreements to meet several strategic goals—including the preservation of a healthy level of independence. *See* BIOTECH 95, *supra* note 2, at 19.

401. *Id.* at 33 ("The pharmaceutical companies have more leverage and can wait for capital-hungry biotech companies to accept lower offers . . . . [B]ig pharma is less willing these days to accept less than worldwide product rights, which makes it more difficult for biotech companies to subdivide their markets for licensing purposes."); Ronald Rosenberg, *Financing of Gene Industry a Tough Sell*, BOSTON GLOBE, May 21, 1995, at 108 (Numerous partnerships with pharmas are being formed, but many genotech companies may be signing oout of desperation.).

to discourage genotech-pharma alliances. Arguably, the alliances create more possibilities than dangers. Instead of developing drugs that merely identify illness and address symptoms, such integrated teams more successfully could research and develop drugs that actually target *and* eliminate illness.[402] Market-driven forces are putting tremendous pressure on the pharmas, thus suggesting that pharmas will not hold back on introducing new technologies.[403] Moreover, to the extent that other sources of United States financing are not reliable in the long-term, the pharmas may offer an alternative to off-shore migration of the technology and foreign acquisition of an industry rooted in the United States economy.[404]

The concern over pharma control also may be misplaced. The alliances may simply buy time for the genotech industry to recover from the inevitable clinical disappointments and regulatory struggles in its present and near future.[405] Many of the genotech firms are structuring multiple deals with different pharmas, each deal built around specific technologies, thereby enabling the genotech firms to maintain a level of independence.[406] To the extent there are concerns that consolidation through alliances with pharmas will have an adverse impact on innovation, federal policy committed to enforcing antitrust laws in the field of genotechnology should address these concerns. In sum, Congress should assess and monitor the economic incentives of the industry, yet refrain from large-scale regulatory changes to control the market beyond those outlined above.

As argued throughout this Article, new regulation to eliminate false barriers to market entry for genotechnologies and to provide consistency between federal R&D policy and policy bearing on commercialization of these technologies needs to be implemented. An effort must be made to coordinate FDA, PTO, NIH and other policy directly bearing upon the industry. Overregulation for its own sake will delay the introduction of technologies without concomitant increases in patient safety, thereby depriving patients of

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402. BOSTON CONSULTING GROUP, INC., *supra* note 12, at 65-67; Ronald Rosenberg, *Taking Gene Therapy to the Market: Biotech Start-ups, Drug Firms Try New Approach*, BOSTON GLOBE, Jan. 22, 1995, at 80.

403. *See* THE BOSTON CONSULTING GROUP, INC., THE CHANGING ENVIRONMENT FOR U.S. PHARMACEUTICALS: THE ROLE OF PHARMACEUTICAL COMPANIES IN A APPROACH TO HEALTH CARE 14-26 (1993).

404. *See* BIOTECH 96, *supra* note 2, at 56 (addressing issue of off-shore migration); *Prepared Testimony of Robert T. Abbott, President and CEO of Viagene, Inc., Before the House Committee on Science, Space and Technology*, Federal News Wire (Fed. Info. Systems Corp.) (Sept. 28, 1994) (foreign acquisition of United States genotech industry potential consequences of current harsh financing climate; pharma company acquisition provides alternative liquidity to traditional public offering).

405. *See* Kaufmann, *supra* note 137, at 1D.

406. *See* BIOTECH 95, *supra* note 2, at 18.

the benefits of new drugs and negatively affecting health costs.[407] As long as the industry is competitive, it will produce drugs efficiently.

Congress must focus on identifying and correcting those situations where the market is imperfect or where other social or ethical concerns compel a different result.[408] If genotech products are held back from the market as a result of federal policy, it must be because they are being fully and efficiently assessed and not because of regulatory shortcomings. Additionally, federal policy must focus not just on the efficacy and safety of the technologies but also on the ethical and social questions they raise.

D. *Ethical Issues*

Like most social and political revolutions, the revolution in health care associated with genotech is accompanied by substantial social and ethical questions.[409] With the United States fostering the growth of a genotech industry and leading the world's efforts in the field of human genetics, it is unconscionable that the United States has not assumed the lead in addressing the ethical implications of these technologies.[410] The reality is that the United States is lagging behind many of its sister nations, including many European nations and their collective conscience as embodied in the European Union, in even *acknowledging* these blatantly obvious issues. Needless to say, therefore, the United States has not begun to address them in a direct and practical manner.[411]

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407. *See* Rob Norton, *History's Lessons of Health Care Costs*, FORTUNE, Dec. 28, 1993, at 86-87 (discussing historical inefficacy price caps); *Four States Driving Up Medical Home Health Care Costs*, HOME HEALTH CARE DEALER/SUPPLIER July-Aug. 1995, at 20 (attributing technology delays to regulatory burdens); *see generally*, THE BOSTON CONSULTING GROUP, INC., *supra* note 12.

408. *See generally* Gorman, *supra* note 16.

409. *See* THE GENETIC FRONTIER: ETHICS, LAW AND POLICY (Mark S. Frankel & Albert Teich eds., 1994); THE ETHICAL DIMENSIONS OF THE BIOLOGICAL SCIENCES (Ruth Ellen Bulger ed., 1993).

410. *See generally* ASSESSING GENETIC RISKS, *supra* note 17.

411. *See* U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, BIOMEDICAL ETHICS IN U.S. PUBLIC POLICY—BACKGROUND PAPER (1993) [hereinafter BIOMEDICAL ETHICS]. Although the United States has attempted to establish ethical guidelines for medical care and research issues (for example, the use of human beings in research), HGP-specific issues have not been adequately addressed even though three percent of the HGP budget is committed to addressing ethics issues through the Ethical, Legal, and Social Issues (ELSI) component of the HGP—the largest source of federal funding for bioethics. *Id.* at 8. *See generally* Malinowski, *supra* note 39.

The fact is that scientists, policymakers and even much of the public have grown too comfortable with science's capabilities in the area of human genetics. When the first gene was cloned in 1972, "scientists were so worried about the implications of what they were doing that they considered a voluntary moratorium on the recombination of cloned genes into the DNA of other organisms. Now, . . . [t]he creation of recombinant people, with foreign genes stitched into their cells, is widely accepted." *Survey*, *supra* note 2, at S4. *But see* Oman, *supra* note 13, at C44 (suggesting that "the United States has been very sensitive" to ethical issues raised by human

Although theoretically sophisticated ethical treatment of the issues raised by genotechnologies may prove helpful, there is an immediate need for *applied* ethics. Many of the societal ramifications of simply not dealing with the ethical aspects of genetics technologies are readily ascertainable. Task forces assembled both by the Institutes of Medicine and HGP have acknowledged that commercial and academic laboratories are making genetic testing capabilities easily accessible to the public too quickly and that many genetic tests are subject to misinterpretation.[412] Legal liability for wrongful birth as well as wrongful life and general malpractice is likely to pressure health care providers to err on the side of making such genotech diagnostics—however imprecise—available.[413]

There also are foreseeable economic consequences associated with these technologies. The lack of adequate consideration of the societal and ethical implications of genotechnologies, and introduction of resulting guidelines and regulations, leave the industry subject to broad-side attacks such as the recent challenge stirred up by an environmental activist, Jeremy Rifkin, and a coalition of conservative religious leaders.[414] Genotech is, in essence, medicinal evolution, and unchecked political controversy could erect high and even impenetrable barriers. For example, in light of the growing dependency

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genetics research).

On the other hand, "[a] recurring theme in most of the academic commentary on the Human Genome Project is the need for community involvement. A recurring complaint is the relative lack of community participation until now." Kirby, *supra* note 33, at 17-19. Concerns have been "expressed about the way in which the Human Genome Project itself has been initiated and funded by governments and scientists with very little input from the public." *Id.* at 14. For an example of European efforts to address the ethical and social implications of genetics technologies, consider that France has proposed uniform legislation to make such issues the matter of true public policy, rather than being determined by individual doctors on a patient-by-patient basis. *Id.; see also* Malinowski, *supra* note 39, at 1513. Also, the Council of Europe is developing a regional convention. *See* Kirby, *supra* note 33, at 18; Richard H. Nicholson, *Old World News: One Law for All?*, HASTINGS CENTER REP., Mar.-Apr. 1995, at 4, 4 (addressing debate whether the proposed European Convention on Bioethics now being prepared by the Council of Europe should be used to enforce moral principles).

412. *See generally* ASSESSING GENETIC RISKS, *supra* note 17; Malinowski, *supra* note 39; Saltus, *supra* note 17.

413. *See* Malinowski, *supra* note 39, at 1504-07.

414. Under the leadership of Rifkin, head of the Foundation on Economic Trends which consistently has opposed genetic engineering research, this alliance of 80 religious leaders asserted the ethical position that patenting basic units of life demeans it; their immediate political objective was to obtain a ban on the patenting of cells, animals and other basic forms of life. Kathleen Day, *Church Groups to Fight Patenting of Life Forms; Coalition to Press for Congressional Action*, WASH. POST, May 13, 1995, at A3; Ronald Rosenberg, *Call to Ban Patents Stirs Industry Fears*, Boston Globe, May 19, 1995, at 39. However, "[m]any genetic scientists and executives themselves say the basic knowledge of the chemical code of life—DNA—should be in the public domain, with patents going only to unique processes and products derived from DNA knowledge." *Id.*

upon European pharmaceuticals,[415] there is a real danger that political controversy in the United States over human genetics could result in a repeat of the RU486 experience, meaning that technologies could be kept out of the consumer market for purely *non*scientific reasons.[416]

Ethical issues are readily apparent in virtually all aspects of the genotech industry and its technologies. These include (1) patient care issues, such as insurance coverage,[417] counseling,[418] cost,[419] accessibility,[420] and

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415. *See* BIOTECH 96, *supra* note 2, at 30. However, 69% of 1995 biotech deals were structured with United States firms. *Id.* at 31.

416. *See generally* Claire L. Ahern, Note, *Drug Approval in the United States and England: A Question of Medical Safety or Moral Persuasion?—The RU-486 Example*, 17 SUFFOLK TRANSNATIONAL L. REV. 94 (1994); LAWRENCE LADER, RU 486: THE PILL THAT COULD END THE ABORTION WARS AND WHY AMERICAN WOMEN DO NOT HAVE IT (1991).

417. The possibility that insurers already are using genetic test results in making health coverage decisions was recognized by Francis Collins at the Sept. 29 hearing of the Senate Career Coalition. *Scientists, Insurers Disagree on Genetics Test Resvex Access*, THE CANCER LETTER, No. 38, Oct. 6, 1995, at 2; *see also* M. A. Dewar et al., *Genetic Screening by Insurance Carriers*, 267 J. AM. MED. ASSOC. 1207, 1207-08 (1992) (letter to the editor); Mark Rothstein, *Genetics, Insurance, and the Ethics of Genetic Counseling*, 3 MOLECULAR GEN. MED. 159-77 (1993). Insurance discrimination based upon genetic predispositions has not been directly addressed by the federal government, with the exception of a recent EEOC decision regarding employment discrimination and not specifically addressing the issue of insurance. *See infra* note 423. However, several states, including Arizona, California, Maryland and Montana are regulating genetics-based insurance discrimination. *See* ARIZ. REV. STAT. ANN. §§ 20-448 (1990 & Supp. 1995); CAL. INS. CODE § 11512.95 (West 1990 & Supp. 1995); MD. ANN. CODE art. 48A, § 223 (1994); MONT. CODE ANN. § 33-18-206 (1993). *See generally Survey*, *supra* note 2, at 15.

418. *See generally*, ASSESSING GENETIC RISK, *supra* note 17; Malinowski, *supra* note 39.

419. Genetics technologies may be more effective, but also more expensive than existing treatments. Accordingly, hospitals, doctors, patients, and insurance companies may find themselves faced with a choice between an affordable traditional treatment and a cutting-edge alternative that offers a marginal advantage at a much higher price. A prime example of this dilemma was the introduction of Genentech's clot-busting drug known as t-PA or Activase. *See Doctors Face Ethical Dilemma Over Which Heart Drug to Use*, OREGONIAN, Sept. 5, 1993, at D4. The drug could save 10 more lives than an existing drug, Streptokinase, for every 1000 heart attack patients treated—a result of 2000 lives/yr. Although Genentech offers the drug free of charge to some needy patients, the cost for t-PA is at least $2000 per patient, while streptokinase costs only $200. *Id.*; Tom Schmitz, *High-Tech Heart Drug Gets Tiny Edge in Study*, SAN JOSE MERCURY NEWS, May 1, 1993, at 1A; Byron Spice, *Costlier Drug is Better for Heart Trouble*, PITTSBURGH POST-GAZETTE, May 1, 1993, at A5. Another cost issue is that, in light of some of the tremendous costs of genetic technologies, it is unlikely that insurance companies will cover them readily and that we as a society can afford them—at least until other costs have been lowered through the technologies. For example, Genzyme's Ceredase/Cerezyme treatment for Gaucher's Syndrome, which afflicts 5000 people worldwide, costs $150,000 a year initially, followed by a maintenance program of monthly infusions for the rest of the patient's life at a cost of approximately $60,000 per year. Ronald Rosenberg, *Genzyme's Plans to Beat Obsolescence*, BOSTON GLOBE, Jan. 8, 1995, at 60. ("Indeed, Genzyme has received some harsh criticism both for the drug's high price—as much as $350,000—when it was first introduced—as well as for its overly aggressive efforts to sell directly to patients."). Such high costs are especially controversial when the underlying research and development was funded in part through federal funds and/or benefitted significantly from federally-transferred technology, or agency resources were expended to expedite review of the technology. *See supra* note 326 (addressing AZT controversy); *see also* note 388 and accompanying text (addressing BRCA1 controversy). The difficult cost-benefit analysis associated

informed consent for both treatment and research;[421] (2) patient rights issues, such as privacy[422] and discrimination;[423] (3) the inherent patient/subject

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with patient accessibility and insurance coverage may, under the Americans With Disabilities Act, be conducted by juries. *See* Howard Schaffner & Monica E. McFadden, *Disabilities Act Makes Denial of Benefits Risky*, NAT'L L. J., Jan. 16, 1995, at C17-19.

420. *See generally Public Priorities for Genetic Services*, HASTINGS CENTER REP., May-June 1995, at S1-23 (Special Supplement). The problem of reasonable and equitable access to genetics technologies; the circumvention of the benefits of such technologies by inadequate laws, public policies, and commercialization which collectively skew equitable distribution; and the issues of informed consent and privacy are addressed in John D. Blum, Book Review, 15 J. LEG. MED. 345 (June 1994) (reviewing EUGENE BRODY, BIOMEDICAL TECHNOLOGY AND HUMAN RIGHTS (1993)). An especially complex issue is the accessibility of investigative treatments for the terminally ill. *See supra* Section III.A (addressed in the context of FDA policy).

421. The impact of genetic diagnostic capabilities on patient care has not been assessed, even though the expansion of these technologies is explosive:

> The current explosive pace of research in the molecular biology of cancer has resulted in a proliferation of new tests. If these are implemented, more and more people will be advised that they have an early cancer and can be treated. Unfortunately, there are indications that finding a cancer early may not be better, unless it is one that will progress if untreated . . . . Aside from the burden of fear and anxiety that accompany a cancer diagnosis, the risk from possibly unnecessary surgery, the patient with an early detected cancer faces the risk of uninsurability due to a pre-existing condition.

Skolnick et al., *supra* note 341, at 2. The issue of consent and confidentiality in the context of research for HGP and HGDP is discussed in Knoppers, *supra* note 164, at 6-15 (discussing and citing international legislation to address these issues).

422. *See generally*, Bartha N. Knoppers, *Confidentiality in Genetic Testing: Legal and Ethical Issues in an International Context*, 12 MED. & LAW 573-82 (1993). The danger of dissemination of genetic information has been acknowledged through the introduction of the Genetic Privacy Act, the first legislation proposed by the Ethical, Legal, and Social Issues (ELSI) component of the Human Genome Project. *See Gene Privacy Act Introduced*, HUMAN GENOME NEWS, Mar.-Apr. 1995, at 4, 4. This Act, which has been introduced into six state legislatures,

> would require explicit authorization to collect DNA samples for genetic analysis, limit uses of the samples for genetic analysis, limit uses of the samples and genetic information obtained from them, and set forth penalties for violators. The act aims to protect individual privacy while permitting genetic analysis for medical and identification purposes and legitimate research.

Id. Legislation to ensure the confidentiality of genetic information also has received public support from powerful legislators, including Senator Barbara Mikulski, a Democrat from Maryland. *See* Bob Hohler, *Congress is Urged to Fund Gene Research in Health Plan*, BOSTON GLOBE, May 14, 1994, at 5. Such legislation has been proposed in the past—the Human Genome Privacy Act (HGPA), which was introduced before the House of Representatives on Sept. 13, 1990; H.R. 5612, 101st Cong., 2d Sess. (1990). *See* George P. Smith & Thaddeus J. Burns, *Genetic Determinism or Genetic Discrimination?*, 11 J. CONTEMP. HEALTH L. & POL'Y 23, 52-57 (Fall 1994). Existing privacy protection is allotted under the Federal Privacy Act of 1974, 5 U.S.C. § 552a (1988), which restricts the type of information the government may collect, explicitly restricting the collection of information by federal agencies. The privacy of patient records in general is addressed in Alison Bass, *HMO to Limit Access to Data: VA Units Take Opposite Tack*, BOSTON GLOBE, Mar. 14, 1995, at 1.

423. *See* EEOC, Directives Transmittal, Executive Summary: Compliance Manual § 902 (Mar. 14, 1995); Richard A. Epstein, *The Legal Regulation of Genetic Discrimination: Old Responses to New Technology*, 74 B.U. L. Rev. 1 (1994); Charles B. Gurd, *Whether a Genetic Defect is a Disability Under the Americans with Disabilities Act: Preventing Genetic Discrimination by Employers*, 1 ANNALS HEALTH L. 107 (1992); Francis H. Miller & Philip A. Huvos, *Genetic*

conflict surrounding patients in experimental clinical trials[424] and those whose DNA is being used for the underlying HGP and HGDP research;[425] (4) professional and business ethics issues, such as pricing[426] and conflicts of interest[427] and allegations of favoritism on the part of the federal

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Blueprints, Employer Cost-Cutting, and the Americans with Disabilities Act, 46 ADMIN. L. REV. 369 (1994); Mark A. Rothstein, *Genetic Discrimination in Employment and the Americans with Disabilities Act*, 29 HOUS. L. REV. 23 (1992). The scope of the danger of discrimination based upon genetic information is immense for, "[a]t some level, there is something in everyone's genome that could get them into trouble eventually." *Survey, supra* note 2, at S15; *see also* Richard Saltus, *US Ruling Bars Discrimination Based on Genes*, BOSTON GLOBE, Apr. 11, 1995, at 5. The policy statement by the EEOC barring discrimination based upon genetic predisposition under the Americans with Disabilities Act reflects a growing recognition of the societal impact of scientific advances. However, this ruling strictly pertains to employment; though most people receive insurance coverage through their employer, the decision does not address insurance issues directly. Under the EEOC's new interpretation, an employer cannot terminate an employee or renege on a job offer because of the results of genetic testing. As for the state level, the California legislature has voted to ban all discrimination on the basis of genetic status. *Survey, supra* note 2, at S15.

424. *See* Margaret Gilhooley, *Innovative Drugs, Products Liability, Regulatory Compliance, and Patient Choice*, 24 SETON HALL L. REV. 1481 (1994) (addressing the conflict between the drug-approval process and patient protection, primarily from the approach primarily of patient care). The dangers associated with clinical trials are exemplified in the chemotherapy incidents at the Dana-Farber Cancer Institute disclosed in spring 1995, the subsequent disclosure of numerous other such incidents at Boston-area hospitals, and the patient deaths and hospitalizations resulting from the Phase III clinical trial administered by Genetics Institute of Cambridge, Massachusetts. *See* David W. Bates et al., *Incidence of Adverse Drug Events and Potential Adverse Drug Events: Implications for Prevention*, 274 JAMA 29 (July 5, 1995); Richard A. Knox & Daniel Golden, *Doctors Missed Clue to Chemotherapy Overdoses*, BOSTON GLOBE, June 19, 1995, at 20; Richard A. Knox & Daniel Golden, *Drug Dosage was Questioned: Dana-Farber Pharmacist Sent Order Back to Doctor in Breast Cancer Case*, BOSTON GLOBE, June 19, 1995, at 1, 20; Richard A. Knox & Brian C. Mooney, *Hospital Dosage Mistakes Not Rare*, BOSTON GLOBE, Apr. 16, 1995, at 1, 14; Richard A. Knox, *Hospital Drugs Hurt 1 in 15*, BOSTON GLOBE, July 5, 1995, at 1, 13 Richard A. Knox, *State Cites Dana-Farber Failures*, BOSTON GLOBE, May 31, 1995, at 2, 28; Ronald Rosenberg, *2 More Hospitalized in Drug Test*, BOSTON GLOBE, June 13, 1995, at 45, 64; Michell Zuckoff, *Drug Inquiry Targets Absence of Use of Test Dose, Waiting Period*, BOSTON GLOBE, June 15, 1995, at 51.

425. *See generally* Knoppers, *supra* note 164, at 6-22.

426. The lack of regulatory control despite extensive federal investments and direct contributions in the underlying technologies have given rise to controversies over pricing and commercialization of technologies, such as the controversies associated with AZT and BRCA1, a gene responsible for approximately half the incidence of hereditary breast cancer or about five percent of all breast cancer diagnosis. *See, e.g.*, Skolnick et al., *supra* note 341. There is ample and persuasive evidence that price caps should be rejected "because they will have devastating effects on innovative *new* drugs and devices." Teisberg et al., *supra* note 384, at 140; *see also* Norton, *supra* note 407. Nevertheless, without measures to alleviate the impression that federal funds are being used to reap huge commercial returns for the industry and at the expense of public health (including more effective and aggressive public relations efforts by the industry), pricing controversies will continue to arise.

427. To the extent that genetics technologies will streamline drug consumption by being more effective and through enhanced diagnostic capabilities, there is an obvious potential conflict associated with the pharma buy-up of genetics technologies. *See* Schrage, *supra* note 73, at 32 ("The more genetic information that's generated, . . . the better tailored and targeted drug therapies will become. Your genetic profile will become an indispensable part of the medications

government,[428] many generated by the direct involvement of researchers in entrepreneurial efforts to raise capital for and commercialize their work;[429] and (5) global issues bearing upon international human rights, such as the impact of the patenting[430] and commercialization of genetics technologies on biodiversity and the environment.[431] Ironically, as suggested above, the most readily available technologies—genetic diagnostic and screening capability—raise many of the most ominous ethical questions. These questions include self-selection, also known as eugenics,[432] and patient care issues such

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you might be prescribed.") (citation omitted).

428. A deluge of such allegations has accompanied the patent granted to Dr. W. French Anderson and his colleagues at the NIH on March 21, 1995, and licensed exclusively to Genetic Therapy Inc. of Gaithersburg, Maryland. *See supra* note 348 and accompanying text.

429. The genotech industry is, by its very nature, a conglomerate of high science and raw venture capitalism, which has given rise to allegations and actual incidents of scientific misconduct and questionable practices. *See, e.g., US Health Officials Criticize Drug Firms Marketing Ethics*, SAN JOSE MERCURY NEWS, Oct. 13, 1994, at 12A (Genentech to stop funding height screening because critics say it was a veiled effort to get short kids to take growth hormone; charges that Genentech executive paid $1 million in kickbacks to Minneapolis doctor); Robin E. Margolis, *Regulatory Update*, HEALTH SPAN, Oct., 1994, at 30 (the Office of Research Integrity at HHS brought allegations of scientist misconduct against BioQuest, Glaxo Institute for Molecular Biology, and Stanford University, alleging that they misstated credentials and fabricated data to obtain grants). Providing scientists and top executives with equity holdings is the only way to attract top-flight people to fledgling firms, which stand a high risk of failure, and the only way to do this is to raise capital premised upon success. The end result may be a hard-sell to investors and pressure and scientists to embellish is its success. *See* Kathleen Day, *Biotech Executives Find Wealth in their Genes*, WASH. POST, April 8, 1994; Fisher, *supra* note 101, at 9A ("[T]he commercial recruitment of leading scientists from publicly supported universities and federally backed genome centers has stirred professional resentment among some geneticists, who argue that the rush to commercialize or patent pieces of the genome project will hinder the greater discoveries that can come when the scientific community freely shares its discoveries."). This is especially troublesome during a time when reported incidents of scientific fraud are becoming more prevalent. *See* Anthony Flint, *US Curbs on Data Fraud Not Expected: Research Institutions Need to Control Problem, Head of Federal Panel Says*, BOSTON GLOBE, Apr. 11, 1995, at 3.

430. Much controversy has surrounded the commercialization of R&D paid for (if not conducted) by the federal government. *See, e.g.*, Skolnick et al., *supra* note 341, at 2-3. The international community has been critical of the NIH's efforts to patent gene sequences despite the theme of international cooperation associated with HGP. *See* Malinowski, *supra* note 89, at 8; *cf.* John Richards, *International Aspects of Patent Protection for Biotechnology*, 4 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 433 (Summer 1993) (citing 23 countries as having specific provisions barring the grant of patents for inventions whose publication or exploitation would be contrary to morality).

431. *See* Goldman, *supra* note 216, at 695; Kirby, *supra* note 33, at 18 ("The greatest care is needed now as we face the possibility of reducing, or even eliminating, elements of [humans' genetic] diversity.").

432. *See generally* Malinowski, *supra* note 39, at 1493-1497. How genetics technology is used, not the technology itself, is the issue, and the capabilities and temptations introduced by genetics technologies are the danger: "To use genetic technology as a way of trying to control what other people will become is not only immoral; it is also to miss the point. The true significance of genetic technology, and the power that it is delivering over life, is not that people can be designed from scratch, but that they can break free from some of the limitations imposed by their inherited genes." *Survey*, *supra* note 2, at S17.

as insurance coverage and access, counseling/informed consent requirements, and increased demand for in-vitro fertilization and late-term abortion.[433]

Perhaps now, when the consensus among policymakers seems to be that health care funding must be cut,[434] the most fundamental ethical and public policy question is, "Who is going to pay for the forthcoming generation of genotechnologies?" The myriad of genotech products and capabilities underscores this question, especially given the fact that there is no cost-effectiveness requirement for drug approval within the United States. Moreover, the American health care culture is such that patients expect technologies with any enhanced efficacy over market substitutes to be made available, and providers generally have been ready to oblige, regardless of cost.[435] As stated above, legal liability has made providers especially willing to make genetic diagnostic capabilities available.[436] Responsive to such pressures, genotech diagnostic products are multiplying and rapidly being pushed into commercialization.

The silence has lingered far too long.[437] These issues must be addressed and governing regulations introduced and enforced. Although the Office of Science and Technology Assessment has proposed the introduction of a National Bioethics Advisory Commission,[438] what is needed is an independent agency.[439] To be more precise, what is needed is a counterpart

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433. The National Advisory Council for Human Genome Research has warned "it is premature to offer DNA testing or screening for cancer predisposition outside a carefully monitored research environment." Richard Saltus, *Plan to Market Tests for Cancer Gene is Hit*, BOSTON GLOBE, Mar. 10, 1994, at 3. The warning, prompted by successes such as discovery of the BRCA1 Gene, "noted that many questions remain unresolved, including whether a person is better off knowing about a future risk if medicine can do little to prevent the disease, and how to avoid genetic discrimination." *Id.* Oncor, a Maryland genotech company, has announced that it will begin offering gene analysis services to families. *Id.* One implication of this technology is increased demand for in-vitro fertilization and late-term abortion. *See Survey*, *supra* note 2, at S17. *See generally* Malinowski, *supra* note 39, at 1451-54.

434. *See generally* PEROT, *supra* note 390.

435. *Id.* at 303. The issue of cost cannot be addressed adequately in this survey article.

436. See Malinowski, *supra* note 39 (addressing "wrongful birth"/"wrongful life" actions).

437. This silence may be due in part to the distinction made between risk assessment and risk management. As explained by Dr. James Dickson, when research (risk assessment) elements of the Public Health Service entered themselves too far into the arena of the management of risk, there can be political repercussions. Telephone Interview with Dr. James Dickson (Aug. 7, 1994).

438. National Bioethics Advisory Commission Proposed Charter, 59 Fed. Reg. 155, at 41584-85 (Aug. 12, 1994). Several commissions have been formed in the past two decades to address bioethics issues. *See* Jay Katz, *Do We Need Another Advisory Commission on Human Experimentation?*, HASTINGS CENTER REP., Jan.-Feb. 1995, at 29, 29. Furthermore, NIH and the Department of Energy each fund Ethical, Legal, and Social Issues (ELSI) programs, which are the largest Federal funding source for bioethics studies. *See* BIOMEDICAL ETHICS, *supra* note 411, at 8. These commissions and programs, lacking the independence proposed above, have either been unsuccessful or unable to withstand political sea changes.

439. *See* Katz, *supra* note 438, at 29-31. For discussion of the creation of such a body within the United States and an actual proposal to do so in France, see Malinowski, *supra* note 39, at 1513-17. *Cf.* Nicholson, *supra* note 411, at 4 (addressing debate on whether or not the

to the FDA and NIH that has as much regulatory authority as those agencies but which is focused on genotechnology and committed to responsible gathering and dissemination of information to enhance public awareness of genotechnology and the development of needed health policy.[440] This agency should be staffed to represent the perspectives and interests of patients, the genotech industry, health care providers and educators, and the insurance industry. It should be made accountable to the public and Congress and vested with enough authority and resources to investigate genotechnologies and directly introduce regulations. Resulting mandates could require the inclusion of provisions within CRADAs which directly address some of the ethical issues identified above by providing added safeguards against irresponsible uses, thereby alleviating public concern.

Of course, the composition and conduct of such an agency would have to be carefully monitored to ensure that it functions effectively and is not captured by industry or used as a showpiece to stifle dissent from groups such as the religious right. It is critical that the recommendations of such an agency be crafted carefully and publicized extensively. Although the alliance nature of the genotech industry suggests that it will be represented by a powerful lobby, the public accountability mandate of the proposed agency and high-profile nature of genotechnology should safeguard against undue industry influence. Tenure limitations on those appointed to guide the proposed agency would provide another safeguard. Moreover, this interdisciplinary approach to health policy decisionmaking has shown potential in the past—though it always has been applied in the context of bioethics. An independent agency could reduce the element of political vulnerability evident in the functioning of previous United States bioethics commissions which were disbanded before accomplishing their stated goals.[441]

Whether through the proposed independent agency or not, the most difficult ethics issues accompanying genetics technologies will be addressed, and that process will result in regulation. At least one proposal for regulation, the Genetic Privacy Act, which was drafted by a team of academics including George Annas and introduced during the spring of 1995, has attracted the attention of some state legislatures.[442] At the present time, approximately twelve states have enacted genetics regulations, including Colorado and New

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proposed European Convention on Bioethics now being prepared by the Council of Europe should be used to enforce moral principles).

440. France already has taken substantial legislative steps to introduce such an institution into its political system. *See* Malinowski, *supra* note 39, at 1513-17.

441. *See* BIOMEDICAL ETHICS, *supra* note 411, at 1-5; Malinowski, *supra* note 39, at 1498-99. An exception is the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, in existence from 1974-87, which is responsible for the ban on human experimentation without the subject's consent. *See id.* at 1498-99.

442. *See generally* DiChristina, *supra* note 24, at 18.

York.[443] Nevertheless, comprehensive legislation must be debated and enacted at the national level. As set forth above, these issues simply are too controversial and obvious to be ignored much longer without significant consequences—especially with more genotechnologies entering commerce. Instituting the proposed agency would enhance the possibility of generating health policy with foresight and thought, rather than leaving it to be addressed by Congress in a reactionary fashion in response to political challenges and public emotion.[444]

If the commercialization of genotechnology is to be slowed down, it should be slowed for policy reasons, not because it is easier to delay market availability than to deal with these technologies. Again, in light of the human health and other societal implications associated with these technologies, ignoring the policy and regulatory questions and shortcomings surrounding genotechnology is, at best, irresponsible. Moreover, the reforms suggested here might inspire members of the genotech industry to better organize themselves, consider more carefully the ethical issues accompanying their work, and—in a constructive manner—make proposals which embody the industry's insight.[445]

Conclusion

Since the beginning of this decade, the front-pages of the nation's major daily newspapers have continuously been occupied by the genotech industry's discoveries. Nevertheless, health policy responsive to practical applications of the resulting technologies is insufficient, especially at the federal level. The nation's policymakers have not addressed issues as obvious and important as insurance coverage for genotech therapeutics and diagnostics, privacy of genetic screening results, and informed consent requirements for genetic screening in a practical manner. Thus, the diagnostics and therapeutics that the genotech industry has been developing over the past several years, which are about to begin reaching the public, are almost as ominous from a health policy perspective as they are inspiring to the patients who will benefit.

Federal policy, to a large extent, has driven the genotech industry to its present cross-roads. Policy supportive of genotech R&D has not been followed by an adequate regulatory and health policy response to commercialization of

443. Colo. Rev. Stat. § 10-3-1104.7 (1994 & Supp. 1995); N.Y. Pub. Health Law § 2733 (1990 & Supp. 1995); *see also* Associated Press, *Geneticist Calls for Privacy in Test Results*, BOSTON GLOBE, Sept. 30, 1995, at 3.

444. *See, e.g.*, *supra* note 414 (addressing recent challenge to patenting of genetic discoveries raised by a coalition of religious leaders and Jeremy Rifkin).

445. The introduction of regulation in the medical profession had a similar effect, inspiring the profession to organize and become central to the health policy of the nation. *See generally* PAUL STARR, THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE (1982).

the resulting products. The industry's accomplishments in science and health care have been achieved by small, entrepreneurial companies aided by the endorsement and direct and generous support of the federal government during the late 1980s and early 1990s. The federal government's public support of HGP also has enabled genotech companies to draw vast amounts of capital from the private sector, thereby directly helping to launch the industry. Unfortunately, federal policy as well as the pharmas' involvement may have created a "false" market built upon inflated and unobtainable expectations, resulting in major disappointments and the loss of investor interest. Investment capital, taxpayer dollars and, more important, invaluable human capital may all have been accessed too early—before the basic research necessary to turn genotechnology into safe and effective products was complete.

Although the market appeal of genotech stock has returned, it is uncertain how long it will remain. The insufficiency of the existing regulatory and legal infrastructure, along with the potential for public concern about drug disappointments and reactionary policymaking, threaten the industry's market appeal and future. When the genotech industry completes the metamorphosis it is currently undergoing, and the industry's first generation of technologies are well within the realm of public awareness, it may be that existing talent and venture capital was spent, and the industry closed a tremendous learning curve only to have its accomplishments purchased cheaply by pharmas or held back by reactionary policymaking.

At the present time, some element of change is certain. How the genotech industry is reshaped, or reshapes itself, will be influenced by federal policy, industry's own successes and failures, interest on Wall Street and among investors in general, and leadership within the industry. In the midst of the present uncertainty, and on the eve of the introduction of practical applications of genotechnologies into commerce, there is an opportunity for policymakers and industry to have a profound impact on human health. The federal government's timely response through the introduction of an adequate regulatory infrastructure could accelerate the availability of genotech products, enhance and stabilize the investment appeal of the industry, ensure a safe level of oversight and responsibility, and avoid some readily apparent potential abuses of genotech capabilities. In light of the profound impact of the underlying technologies on human health, the United States' economy, and the United States' overall vested interest in the genotech industry, this opportunity is accompanied by an obligation to assess the adequacy of existing federal policy regarding the commercialization of genotechnologies. Though delays in market availability may be necessitated by direct and thoroughly contemplated policymaking, such delays should not be tolerated when due to regulatory inefficiencies and non-responsiveness.

The problem is that this opportunity to maximize the benefits from

genotechnology in the near future is not discernible without foresight—the same level of foresight shared by the scientists and venture capitalists responsible for the evolution of the genotech industry and advent of practical applications of genotechnologies. Unfortunately, despite the significant role that lawyers are playing in the unfolding of the genotech industry,[446] lawmakers historically have been blind to such opportunities. As recognized and stated by Justice Warren Burger more than a quarter-century ago, "[t]he law does not search out as do science and medicine; it reacts to social needs and demands."[447]

Federal policy has expanded and augmented scientific and medical research resulting in a great number of new technologies. However, existing federal policy is no longer adequate. The gap between genotechnologies and the regulatory infrastructure bearing upon the introduction and uses of genotechnologies has broadened. Before elected public policymakers can thoroughly address and question the uses of genotech therapeutics and diagnostics, health policy will be determined by health care providers on a technology-by-technology, patient-by-patient basis. Another possibility is that public anxiety will trigger short-sighted policymaking which may extinguish commercial incentives and generally prevent future commercial applications of genotechnology.

The lack of regulatory foresight and infrastructure should make both the genotech industry and those who would benefit from the forthcoming generation of genotech therapeutics and diagnostics—all of us—uncomfortable, if not downright anxious. Without regulatory foresight, the industry is more likely to suffer a broad-sided political attack, as exemplified by the recent challenge to the patenting of genetics discoveries launched by a coalition of some eighty religious leaders—the first substantive political challenge to the genotech industry, but certainly not the last.[448] The danger is that the

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446. Law and lawyers are heavily involved in the genotech industry's development, though their involvement is reactionary:

> [L]aw and lawyers are playing a significant role in biotechnology's development. The case for that proposition is clear. Biotechnological product development has a relatively uniform "life cycle," beginning with "conception" in the research of universities and other not-for-profit institutions and "growing" through licensing and technological transfer, patenting, and financing, maturing through regulatory approval, and sometimes dying an "unnatural" death through product liability, rather than in the old-age of obsolescence. With a life-cycle constrained by legal and regulatory events, the law and lawyers play an indispensable role in facilitating every stage of the development of biotechnology.

Robert A. Bohrer, *Forward: What is Biotechnology and Why Devote a Law Review Symposium to Biotechnology Law?*, 55 U. PITT. L. REV. 607, 608-09 (1994) (footnotes omitted).

447. Warren E. Burger, *Reflections on Law and Experimental Medicine*, 15 UCLA L. REV. 436, 436 (1967).

448. *See* Rosenberg, *supra* note 414. With the absence of regulatory lines (whether drawn by legislators or the industry itself), the industry is subject to broad-sided attacks

economic and health care contributions of the industry will be delayed, if not lost.

This Article has described the genotech industry and the forthcoming generation of products it is developing, highlighted critical legal issues which bear upon the industry and its potential contributions to human health, identified important choices which policymakers should address, and offered suggestions to help maximize the human health and economic contributions of the genotech industry. Hopefully, a reasoned debate of these proposals by policymakers will translate into a thoughtful, not reactionary, legal response to genotechnology, thus leading to greater market efficiency and, even more important, alleviation of human suffering and preservation of human life. In light of genotechnology's potential, policymakers must not ignore the choices identified throughout this Article, for we all will bear the significant costs of their silence.

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grounded in legitimate concerns that the societal implications of the technologies have not been considered and addressed. Another example of the cost of lack of foresight is the pricing controversy regarding the anti-HIV drug AZT. Responding to pressure from interest groups, the FDA rocketed AZT—partially developed in NIH laboratories—to market in record time (by cooperating and doubling its staffing), only to unleash hostility from the same interest groups upset with AZT's price. Congress, furious that the federal government had invested so much in a drug that was prohibitively expensive, pressured NIH to include a "reasonable prices" clause in its CRADAs—a clause the NIH's advisory councils now are pressuring the NIH to drop on the grounds that it is impeding the advancement of technologies. BERGLUND & COBURN, *supra* note 183, at 219, 486-91, 513-19, 521-22, 523-24, 548-53 (1995); *see also NIH Should Rethink Pricing Clause*, 372 NATURE 488 (1994).

APPENDIX I:[449]

Biotech Drugs Approved by the FDA by March 1995

Product	Company	Application (use)	Approval Date
Actimmune (gamma interferon)	Genentech	management of chronic granulomatous disease	Dec. 1990
Activase (recombinant alteplase)	Genentech	acute myocardial infarction; acute pulmonary embolism	Nov. 1987 June 1990
Adagen (adenosine deaminase)	Enzon	treatment of infants and children with severe immunodeficiency	March 1990
Alferon N (Interferon Alfa-N3, Human Leukocyte Derived)	Interferon Sciences	genital warts	Oct. 1989
Betaseron (recombinant interferon beta 1-B)	Berlex Laboratories/ Chiron	relapsing, remitting Multiple Sclerosis	Aug. 1993
Ceredase/Cerezyme (alglucerase)	Genzyme	Type 1 Gaucher's disease	Apr. 1991 (Ceredase) May 1994 (Cerezyme) (alglucerase)
Epogen/Procrit (erythropoietin)	Amgen/Ortho Biotech	(Epogen) treatment of anemia associated with chronic renal failure and anemia in Retrovir-treated HIV-infected patients/ (Procrit) chemotherapy-associated anemia	June 1989 Dec. 1990

449. Compiled from data provided by Kendall Strategies Inc.

Humatrope/Nutropin (somatropin)	Eli Lilly/ Genentech, Inc.	human growth hormone deficiency in children/(Nutropin) growth hormone failure due to chronic renal insufficiency prior to kidney transplantation	March 1987 Nov. 1993
Humulin (recombinant human insulin)	Eli Lilly	diabetes	Oct. 1982
IntronA (alpha-interferon)	Schering/Plough	hairy cell leukemia; genital warts; AIDS-related Kaposi's sarcoma; non-A, non-B hepatitis; hepatitis B	June 1986 June 1988 Nov. 1988 Feb. 1991 July 1992
Leukine (yeast-derived GM-CSF)	Immunex	autologous bone marrow transplantation	March 1991
Neupogen (Filgrastim)	Amgen	chemotherapy-induced neutropenia; bone marrow transplant; accompanied neutropenia	Feb. 1991 June 1994
Oncaspar (pegaspargase)	Enzon/Rhône-Poulenc Rorer	acute lymphoblastic leukemia	Feb. 1994
Orthoclone OKT3 (Muromonab-CD3)	Ortho Biotech	reversal of acute kidney transplant rejection	June 1986
Proleukin, IL-2 (Aldesleukin)	Chiron	treatment of kidney (renal) carcinoma	May 1992
Protropin (Somatrem, Human Growth Hormone)	Genentech	growth hormone inadequacy	Oct. 1985
Pulmozyme (DNase)	Genentech	Cystic Fibrosis	Dec. 1993
Recombinate rAHF/Kogenate (recombinant antihemophilic factor)	Baxter Healthcare/ Miles	blood clotting factor VIII for the treatment of hemophilia A	Dec. 1992 Feb. 1993

Recombivax/ Engerix-B (Hepatitis B Vaccine Recombinant)	Merck/ SmithKline Beecham	hepatitis B vaccine	July 1986 Sept. 1989
ReoPro (Abciximab)	Centocor, Inc.	reduce acute blood clot related complications for high-risk angioplasty patients	Dec. 1994
Roferon-A (recombinant alfa-interferon)	Hoffmann-La Roche	hairy cell leukemia; AIDS-related Kaposi's sarcoma	June 1986 Nov. 1988

Appendix II:[450]

Significant Biotech Approvals From July 1994 Through June 1995

Company	Product	Indication	Date
ALZA	DynaCirc CR	controlled release formulation of antihypertensive drug	July 1994
Hybritech	Tandem PSA	detect prostate cancer	August
Molecular Biosystems	Albunex	ultrasound contrast agent, heart disease	August
DNX	BIODIGM	LDL reduction	September
Quadra Logic Technologies	Photofrin	photosensitive drug for photodynamic therapy	September
SangStat Medical	PRA-STAT	HLA antibody detection	October
Amgen	Neupogen	severe chronic neutropenia (3rd indication)	December
Centocor	ReoPro	anti-platelet for angioplasty	December
Epitope	OraSure	oral fluid collection for HIV-1 antibody testing	December
Immunex	Thioplex	cancer (tumors)	December
Univax Biologics	WinRho SD	blood clotting disorders; suppress Rh isoimmunization in pregnancy	March 1995
Bio-Technology General	Bio-Tropin	recombinant growth hormone	May
T Cell Sciences	TRAX CD4 Test Kit	CD4 cell enumeration	May
GeneTrak	CQuentials DR DNA Typing Kit	transplant donor tissue analysis	June

450. Reproduced from BIOTECH 96, *supra* note 2, at 20.

NeXstar	DaunoXome	advanced, AIDS-related, Kaposi's sarcoma	June
U.S. Bioscience	Ethyol	prevent kidney damage in ovarian cancer patients treated with cisplatin	June