THE HUMAN GENOME: A PATENTING DILEMMA

INTRODUCTION

In June, 1991 the National Institutes of Health (NIH) filed a patent for 351 human gene fragments sequenced in the laboratory of NIH scientist Craig Venter. A continuation-in-part application, covering an additional 2,000 fragments and their associated genes, was filed by NIH shortly thereafter. At the same time, Dr. Venter announced plans to sequence every active gene in the human brain.

The issue as to whether patent rights should be granted for this discovery is exceedingly complicated. This is because the NIH researchers do not know the biological functions of the genes they have claimed. Nonetheless, NIH's broad patent claims to the partial gene fragments and to the complete genes encompassing each fragment could conceivably give it control over any medical product developed using the patented genes. Thus, this single patentee could have legal control over a large area of biomedical research and development. As a result, NIH's decision to file for these patents has created a storm of controversy among scientists and members of the biotechnology industry. In addition, the filing has engendered a debate among patent lawyers who have expressed divergent views.

1 NIH is the predominant government agency involved in biomedical research.
3 A continuation-in-part application may give the later claimed inventions the benefit of the earlier filing date. 35 U.S.C. §120 (1988).
5 For a complete description of the relationship between DNA sequences and genes, see JAMES D. WATSON ET AL., MOLECULAR BIOLOGY OF THE GENE, Ch. 1 (4th ed. 1987).
6 In brief, the genetic information in each cell resides primarily in the DNA that is a component of chromosomes. This genetic information is encoded in the sequence of the four different nucleotide bases that are linearly and irregularly distributed along each chain of a DNA molecule. The sequence of bases along a given length of DNA serves as a template to make messenger RNA (mRNA), another nucleic acid which is found primarily in the cytoplasm of the cell. In turn, the mRNA transcripts serve as templates for protein synthesis.

Each gene consists of a number of codons. A codon is a sequence of three nucleotide bases that either specifies a particular amino acid in the protein molecule encoded by that particular gene or acts as a signal to terminate the synthesis of the encoded protein. Thus, one can predict the order of amino acids in a given protein if one knows the sequence of bases in the DNA that codes for that protein. Conversely, one can predict the sequence of bases in a given gene if one knows the order of amino acids in the protein encoded by that gene.

6 Leslie Roberts, Genome Patent Fight Erupts, 254 SCIENCE 184 (1992). Estimates indicate that Dr. Venter can sequence 1,000 to 2,000 fragments each month. See POSITION PAPER, supra note 2, at 3.

Of the 50,000 to 100,000 active genes found in the human genome, approximately 30,000 are expressed in brain. J. G. Sutcliffe, 11 ANN. REV. NEUROSCIENCE 157 (1988).

9 See POSITION PAPER, supra note 2.
on whether and when private intellectual property rights in such knowledge should be granted. Further, several federal agencies have formed a group to determine how the U.S. patent laws apply to this research.  

Although the Patent and Trademark Office (PTO) rejected NIH's initial application, Dr. Bernadine Healy, the director of NIH, is optimistic that many of the PTO's objections can be overcome. Indeed, many who object to NIH obtaining proprietary rights for this information hope that the agency continues to pursue the patent, thus allowing the judiciary an opportunity to clarify the issues raised by this application.

This Comment will address the conflict between the U.S. patent laws and biotechnology by focusing on the NIH patent application. The first part of this Comment discusses the objectives and statutory requirements of the patent system, which the NIH application purportedly did not meet. Next, this Comment focuses on the debate between NIH and its detractors. It explains NIH's reasons for its actions and discusses the criticisms leveled at the agency. Finally, this Comment presents solutions to the problems that have been uncovered by this debate regarding the patentability of genes.

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10 See Opinion Editorial, supra note 8, at A26.
12 See Leary, supra note 7, at B26. Dr. Healy's spokeswoman said that NIH had sent the PTO opinion to outside counsel, who advised her that an initial rejection is commonplace and that the rejection could be overcome.

If an applicant chooses not to answer the patent examiner's objection within six months, the PTO considers the application abandoned. 35 U.S.C. §133 (1988). If the applicant responds and the PTO rejects it a second time, the applicant may then appeal the decision to the Board of Patent Appeals and Interferences. 35 U.S.C. §134 (1988). If the applicant finds the decision of the Board of Appeals unsatisfactory, it may then appeal to the United States Court of Appeals for the Federal Circuit. 35 U.S.C. §141 (1988). The Federal Circuit was created by the Federal Courts Improvement Act of 1982, Publ. L. No. 97-164, 96 Stat. 25 (codified as amended in scattered sections of 28 U.S.C.). Those who argued for establishing a specific court to handle patent cases felt a need for increased stability and predictability of patent doctrine. Robert P. Merges, Commercial Success and Patents, 76 CAL. L. REV. 805, 821 (1988). Although the Supreme Court has the final word on patent law, it has heard very few patent cases since the formation of the Federal Circuit. See, id. at 820 n. 58. However, the Supreme Court still could decide to review the issues raised by the NIH case.

13 The Department of Health and Human Services (HHS) has approved NIH's request to appeal the preliminary ruling. Christopher Anderson, NIH to Appeal Patent Decision, 259 SCIENCE 301, 302 (1993).
16 See infra text accompanying notes 164-212.
17 See infra text accompanying notes 213-257.
18 See infra text accompanying notes 258-313.
THE HUMAN GENOME

THE PATENT SYSTEM: OBJECTIVES AND STATUTORY REQUIREMENTS

Purpose

Article 1, section 8, clause 8 of the United States Constitution grants Congress the power "to promote the Progress of Science and the useful Arts" by offering inventors a limited monopoly on their inventions.\(^{19}\) Under this limited monopoly, an inventor can exclude others from making, using or selling the invention for a set period of time.\(^ {20} \) Several mechanisms explain how patents promote the progress of science. First, the promise of a patent acts as an incentive to invent.\(^ {21} \) Without this promise, an inventor might not be willing to risk the "enormous cost in terms of time, research and development."\(^ {22} \) Second, patents promote disclosure of inventions to the public because patent laws require a full and clear description of the invention\(^ {23} \) so that others can use and make it after the patent has expired.\(^ {24} \) Without patent protection, inventors might otherwise be tempted to keep the details of their invention secret to avoid competition.\(^ {25} \) When the information contained in the patent is added to the "general store of knowledge," it presumably "stimulate[s] ideas and the eventual development of further significant advances in the art."\(^ {26} \) In addition, the patent system fosters capital investment in research.\(^ {27} \) Ultimately, the hope is that "the productive effort thereby fostered will have a positive effect on society through the introduction of new products and processes of manufacture into the economy and the emanations by way of increased employment and better lives for our citizens."\(^ {28} \)

Statutory Requirement §101: Patentable Subject Matter

Congress first enacted legislation to implement the patent system in 1790\(^ {29} \) and most recently amended the full set of statutory requirements for obtaining a patent in 1952.\(^ {30} \) Section 101 of the Patent Act defines patentable subject matter as "any new and useful process, machine, manufacture, or composition of matter,

\(^{19}\) U.S. CONST. art 1, §8, cl. 8.
\(^{24}\) Kewanee, 416 U.S. at 480.
\(^{26}\) Kewanee, 416 U.S. at 481.
\(^{29}\) Act of April 10, 1790, ch. 7, 1 Stat. 109 (repealed 1793).
or any new and useful improvement thereof." In contrast to most foreign patent statutes, §101 does not expressly exclude particular categories of subject matter from patentability. Exclusion is relegated to the judiciary.

Because human genes reside in every cell of every human being, theoretically, one might argue that the DNA sequences which encode human genes are not new compositions of matter and therefore are non-patentable under §101. Indeed, the Supreme Court in Funk Brothers Seed Co. v. Kalo Inoculant Co., held that patents could not be issued for "the discovery of the phenomena of nature." In Funk Brothers, the plaintiff held a patent on a mixed culture of different strains of bacteria which could be used to promote fixation of nitrogen by leguminous plants. The different species of bacteria existed independently in nature and had been available separately in the market. The patentee's contribution had been to discover specific strains of each species that could be mixed together without inhibiting each other. The Court invalidated the patent because the bacteria in the mixed culture "serve the ends nature originally provided and act quite independently of any effort of the patentee.

By analogizing naturally-occurring DNA sequences to the bacteria in Funk Brothers, one could argue that the gene fragments discovered by Dr. Venter are phenomenon of nature and therefore nonpatentable. However, one could also analogize "isolated" DNA sequences to purified pharmaceutical products which the courts have found to be patentable. In cases regarding the patentability of these pharmaceutical products, the courts have distinguished between patentable subject matter and nonpatentable products of nature primarily by focusing their inquiry on whether the claimed invention is the result of human intervention.

Many pharmaceutical products occur in nature in an impure form, which renders them unsuitable for public use. If a patentee isolates and purifies these products to the extent that they are now available for public use, the courts tend to allow patents for these "products of nature." The first of these patents was is-

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32. See generally STEPHEN A. BENT ET AL., INTELLECTUAL PROPERTY RIGHTS IN BIOTECHNOLOGY WORLDWIDE (1987) (providing statutes from various foreign nations).
33. Only 2-3% of the total DNA sequences in the human genome code for genes. Leslie Roberts, Gambling on a Shortcut to Genome Sequencing, 252 SCIENCE 1618 (1991).
34. 333 U.S. 127, 130 (1948).
35. Id. at 128.
36. Id. at 129.
37. Id. at 128.
38. Id. at 131 (emphasis added).
39. See infra text accompanying notes 40-47.
40. See, e.g., In re Bergstrom, 427 F.2d 1394 (C.C.P.A. 1970) (pure prostaglandins isolated from nature patentable as new product); In re Kratz, 592 F.2d 1169 (C.C.P.A. 1979) (pure form of strawberry flavor patentable). "[P]ure materials necessarily differ from less pure or impure materials ... [hence] 'pure' materials are 'new' with respect to them." Id. at 1173 (quoting In re Bergstrom, 427 F.2d 1394, 1401 (C.C.P.A. 1979)).
sued to Parke-Davis for purified adrenalin.\textsuperscript{41} Previously adrenalin had been available for use only as a component of powdered adrenal gland tissue.\textsuperscript{42} Because the purified adrenalin was free of potentially harmful contaminants, the court held that "it became for every practical purpose a new thing commercially and therapeutically."\textsuperscript{43} Similarly, the inventors in \textit{Merck & Co. v. Olin Mathieson Chemical Corp.}\textsuperscript{44} obtained a patent on purified vitamin B\textsubscript{12}. Although Vitamin B\textsubscript{12} occurs naturally in cattle livers and certain microorganisms, the court upheld the validity of the patent because the purified product was superior to the vitamin B\textsubscript{12} available from cattle because of its abundant supply, cheap price, and superior efficiency.\textsuperscript{45} The Court of Appeals for the Fourth Circuit noted that "the step from complete uselessness to great and perfected utility is a long one"\textsuperscript{46} and that "nothing in the language of the [Patent] Act precludes issuance upon a product of nature when it is a 'new and useful composition of matter.'"\textsuperscript{47}

In \textit{Diamond v. Chakrabarty}, the Supreme Court agreed that §101 should be given a broad construction.\textsuperscript{48} The issue in \textit{Chakrabarty} was whether a living organism is patentable subject matter.\textsuperscript{49} On the basis of the language used in §101 and the legislative history of the 1952 Patent Act, the Court found that Congress intended patentable subject matter to include "anything under that sun that is made by man."\textsuperscript{50} Thus, even living organisms could be patented,\textsuperscript{51} as long as man had intervened to make them "different" and to give them "the potential for significant utility."\textsuperscript{52} The Court also declared that Congress could amend the statute if it wanted to exclude such inventions from patent protection.\textsuperscript{53}

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\textsuperscript{41} Parke-Davis & Co. v. H.K. Mulford Co., 190 F. 95 (C.C.S.D.N.Y. 1911) \textit{modified} 196 F. 496 (2d Cir. 1912).
\textsuperscript{42} \textit{Id.} at 103.
\textsuperscript{43} \textit{Id.} (emphasis added).
\textsuperscript{44} 253 F.2d 156 (4th Cir. 1958).
\textsuperscript{45} \textit{Id.} at 161.
\textsuperscript{46} \textit{Id.} at 164.
\textsuperscript{47} \textit{Id.} at 161.
\textsuperscript{49} \textit{Id.} The examiner had rejected the applicant's claim to a bacterium into which the applicant had inserted a foreign gene. \textit{Id.} at 306.
\textsuperscript{50} \textit{Id.} at 309.
\textsuperscript{51} When foreign genes are inserted into the germ cells, i.e. eggs or sperm, of a different species of animal, that animal will pass on the newly-integrated gene to its progeny. Animals that have been permanently altered in this way are called transgenic. BRUCE ALBERTS ET AL., MOLECULAR BIOLOGY OF THE CELL 268-269 (2d ed. 1989).
\textsuperscript{52} \textit{Chakrabarty}, 447 U.S. at 310. The genetically-engineered bacterium claimed by the patentee had acquired the ability to degrade several components of crude oil and had the potential to be useful for cleaning oil spills. \textit{Id.} at 305.
\textsuperscript{53} \textit{Id.} at 318.
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By focusing on the efforts of inventors to isolate DNA sequences with new technological pharmaceutical uses, the courts have found that purified genes are also patentable subject matter. Thus, in Amgen, Inc. v. Chugai Pharmaceutical Co., the district court upheld the validity of claims of U.S. Patent 4,703,008 to purified and isolated DNA sequences of erythropoietin (EPO). The court did not agree with the defendant that the claimed invention was the DNA sequence encoding EPO and therefore a "nonpatentable natural phenomenon." Rather, the court construed the claim as limited to the "purified" and "isolated" sequence.

Since the decision in Diamond v. Chakrabarty, the PTO has granted patents on various isolated and purified human genes. Similarly, in the present case, the PTO did not reject the NIH application under 35 U.S.C. §101 because the claims pertained to nonpatentable subject matter. Rather the application was rejected due to lack of utility.

Statutory Requirement §101: Utility

The PTO rejected NIH's application under 35 U.S.C. §101 because the claims purportedly lacked patentable utility. Because few people go to the trouble and expense of applying for a patent on a useless product, the PTO seldom denies patent protection on this basis. This is especially true for mechanical and engineering patents.

The PTO cannot refuse a patent on a product having only one use. In addition, patent protection for a product is not limited to the use described in the patent, but will encompass any future use that may be found for that product. However, because the usefulness must be definite and known at the time the application is filed and not contingent upon further research, the utility requirement presents a greater problem for inventors of chemical or biotechnological

55 Id. at 1759.
56 Id.
57 See, e.g., U.S. Patent No. 4,370,417 (claiming DNA sequence for plasminogen activator protein); U.S. Patent No. 4,713,332 (claiming DNA sequence for human T cell antigen receptor); U.S. Patent No. 5,164,369 (claiming DNA sequence for human alveolar lung surfactant); U.S. Patent No. 5,166,058 (claiming DNA sequence for human osteoinductive proteins); U.S. Patent No. 5,171,680 (claiming DNA sequence for human superoxide dismutase).
59 See id.
60 See Eisenberg, supra note 14, at 905.
63 Id.
64 In re Kirk, 376 F.2d 936, 945 (C.C.P.A. 1967).
products who often cannot predict the biological effectiveness of a product without extensive research. Thus, in *Brenner v. Manson*, the Supreme Court invalidated a patent for a new process for making steroids because the patentee had not shown any utility for the steroids synthesized by the process. Explaining that a patent is not a "hunting license," the Court found that the patentee's claim that the compound could be useful some day was insufficient to satisfy the utility requirement. Reasoning that Congress was unwilling to grant a monopoly to an inventor unless the public received a benefit from the invention, the Court found that a patent is "not a reward for search but compensation for a successful conclusion." Thus, a product that is solely an object for "use-testing" should not be granted a patent.

When NIH filed its present application, it had no idea of the biological function of the numerous genes it is seeking to patent. This is because biotechnology has not reached the stage where one can predict the function of a protein encoded by a gene on the basis of sequence information alone. Since the applicant in *Brenner* was not able to patent a new steroid without an identifiable use, theoretically NIH should not be able to patent a DNA sequence without identifying its use. In fact, many patent lawyers predicted that the NIH application would fail for lack of utility.

Anticipating this objection, NIH identified several different general uses for the sequences, including use as genetic markers for tissue typing or forensic identification. In its application, NIH also stated that the partial sequences could be used to probe for complete genes that are actively being transcribed in brain. Even though this represents a greater showing of utility than that made by the patent applicant in *Brenner*, the PTO rejected several claims of the NIH patent because they lacked substantial utility. The examiner agreed that the sequences

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67 Id. at 536.

68 Id.

69 Id. at 535.

70 See Roberts, supra note 6, at 184.


73 See Ginsberg, supra note 4, at 1. A number of attorneys also predicted that the application would not pass the requirement of nonobviousness.

74 *Venter Application* at 6 (November, 1990) (A redacted copy of the 1990 Application was provided by the Industrial Biotechnology Association, 1625 K Street, N.W., Suite 1100, Washington, D.C. 20006-1604).

75 Id. at 3-4.

76 See Eisenberg, supra note 14, at 905.

could be hybridized to a variety of different preparations of other nuclein acids. However, the examiner noted that one of skill in the art would not understand the significance of any result of such a hybridization because the application did not provide a basis for interpreting these putative results. Because it would be necessary to do further work in order to establish substantial utility for the sequences disclosed in the application, the PTO rejected the application under §101.

Statutory Requirement §102: Novelty

The requirements for novelty are set forth in §102 of the Patent Act. In essence, the novelty requirement means that an invention is patentable only if it was not previously produced or described. The underlying rationale for this requirement is that an inventor should not be permitted to monopolize something that already exists in the public domain. However, under §102, a patent cannot be denied or invalidated unless each and every element of the claim invention is disclosed in a single prior art reference. If every element is found in a single prior art disclosure, the invention is anticipated. Usually, a patent-applicant for a biotechnology invention can avoid problems with anticipation if he diligently defines the differences between the invention and the prior art.

Even though a first inventor has publicly disclosed his invention prior to filing an application, he may obtain a patent in the United States as long as the application is filed within one year of the date of disclosure. This one year grace period is unique to the United States and a few foreign countries.

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79 See, id. at 6.
82 Specifically, the pertinent parts of §102 state:
   A person shall be entitled to a patent unless -
   (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
   (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for the patent in the United States. . . .
85 Diversitech Corp. v. Century Steps, Inc. 850 F.2d 675, 677 (Fed. Cir. 1988).
89 See Ihnen, supra note 61, at 411 n. 28.
foreign countries a disclosure prior to filing a patent application will bar obtaining a patent.  

In the present case, the PTO found that several claims of the NIH application were so broad, vague and indefinite that they embraced the "cDNA libraries" which the inventors purchased from the biotechnology company Stratagene for use in their experiments. Accordingly, the PTO rejected these claims as being anticipated under §102(b) in that the claimed invention was known or used by others in this country before NIH's invention.

Statutory Requirement §103: Non-obviousness

Prior to 1850, the only requirements for obtaining a patent were novelty and utility. In 1850, the Supreme Court added a new hurdle to patentability in *Hotchkiss v. Greenwood*. The patentee in Hotchkiss had applied an old method for making wood cabinet knobs to the making of clay knobs. Finding that the process lacked "that degree of skill and ingenuity which constitute essential elements of every invention," the Court invalidated the patent. This vague concept of inventiveness was applied inconsistently in the cases that followed. In an attempt to clarify this judicially-created test, Congress added the §103 requirement for non-obviousness to patent law in 1952. This statutory requirement is as follows:

A patent may not be obtained if the differences between the subject matter sought to be patented and the prior are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

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90 Because NIH did not want to lose its foreign patent rights, it filed its application shortly before Venter published the results of his experiments and added the sequences to the GenBank. See Ginsberg, supra note 4, at 2.
91 To prepare the cDNA library it sold to Venter, Stratagene first isolated mRNA from brain tissue. The genetic information encoded in each isolated mRNA molecule was then copied into a complementary DNA (cDNA) replica. For a description of the process, see Watson, supra note 5, at 610.
92 Because mRNA molecules are transcribed from active genes only, the library or collection of cDNA's produced by Stratagene theoretically contains all the genes that are switched on in brain at a particular time prior to isolation of the mRNA molecules. See Roberts, supra note 33, at 1618.
95 52 U.S. (11 How.) 248 (1850).
96 Id. at 248.
97 Id. at 267.
98 See Merges, supra note 12, at 813.
Non-obviousness has been called the ultimate condition of patentability because this requirement determines whether a new and useful invention is a significant enough advance in the art to merit a patent. The underlying rationale for this additional requirement is to prevent issuance of a patent which, in effect, removes existent knowledge from the public domain.

In Graham v. Deere, the Supreme Court formulated a three-part test that judges and patent examiners employ to determine whether an invention meets the non-obviousness requirement. First, the judge or patent examiner must determine the scope and content of the relevant teachings that existed at the time of invention. Second, he must determine the differences between the prior art and the claims of the new inventions. Third, he must assess the ordinary skill of one engaged in the pertinent art. Even though obviousness is assessed on the basis of one having ordinary skill, this hypothetical "ordinary" artisan is familiar with all the relevant prior art. Thus, if one of ordinary skill has all the teachings of the relevant references before him and is able to produce the item defined by the claims, the invention is obvious and non-patentable. However, the examiner or court is not to use hindsight in finding the claimed invention obvious. The Supreme Court indicated that secondary considerations, such as commercial success, long felt need for the invention and failure of others to discover it, can serve as objective evidence of non-obviousness. Recently, the Federal Circuit Court indicated that the examiner or court must consider such evidence if it is available.

102 See Merges, supra note 12, at 812.
104 Id. at 17.
105 Id. at 17. The "scope of prior art" refers to any references that are reasonably pertinent to the particular problem that the invention addresses and may include publications, common knowledge in the pertinent field, and prior patents. Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1535 (Fed. Cir. 1983) (emphasis added).
106 Graham, 383 U.S. at 17.
107 Id. The court or examiner may consider several factors in determining the level of ordinary skill in the pertinent art including 1) the education level of the inventor; 2) the type of problems encountered in the art; 3) prior solutions to those problems; 4) the rapidity with which innovations are made; 5) the sophistication of the technology; and 6) the education level of persons in the art. Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 696 (Fed. Cir. 1983), cert. denied, 464 U.S. 1043 (1984).
109 Id.
110 W. L. Gore & Assocs. V. Garlock, Inc. 721 F.2d 1540, 1553 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984). In Gore, the district court erroneously combined the individual, naked parts of separate prior art references to recreate Dr. Gore's invention even though these references never suggested that such an invention could be made and, in fact, taught against making the inventions. Id. As a result, the Federal Circuit Court found that the lower court had flen "victim to an insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." Id.
There are three cases in which the Federal Circuit has provided insight into the proper test for obviousness regarding biotechnology patents. In *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, the Federal Circuit reversed a lower court decision invalidating the plaintiff's claims on the basis of obviousness. U.S. patent 4,376,110 granted to the plaintiff was a process patent for a "sandwich assay" using monoclonal antibodies to detect corresponding antigens in fluid samples. The prior art taught the use of polyclonal antibodies in similar "sandwich assays" and ways to prepare monocloned antibodies were well known. The Federal Circuit found that the prior art merely invited one to try monoclonal antibodies in immunoassays and did not "suggest how that end might be accomplished." The court also referred to the commercial success of the plaintiff's assays and the unexpected advantage of these assays over previous procedures using polyclonal antibodies as secondary considerations that bolstered the finding of non-obviousness.

In the subsequent case of *In re O'Farrell*, the Federal Circuit upheld the examiner's rejection of patent claims for a recombinant DNA method of producing proteins in bacteria on the grounds of obviousness. The cited prior art included a journal article co-authored by two of the three co-inventors and published more than one year earlier. The major difference between the cited reference and the new claims was substitution of a protein-encoding gene for the frog ribosomal RNA gene that had been inserted into the expression vector in the

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114 In a sandwich assay, the antigen which is present in a fluid sample is first bound to a radioactively labeled monoclonal antibody and then to an unlabeled second monoclonal antibody which is bound to a solid carrier. After the solid carrier is separated from the fluid sample, the amount of radiolabeled material bound through the sandwich (radiolabeled antibody-antigen-unlabeled antibody) to the carrier is determined. This enables the investigator to calculate the amount of antigen present in the fluid. *Hybritech*, 802 F.2d at 1371.

115 Antibodies are the essential elements of the body's immune system and are used to detect and quantify various antigens. Monoclonal antibodies are produced by a clone of cells from a single antibody secreting B lymphocyte. See, ALBERTS, supra note 51, at 177.

116 Id. 802 F.2d at 1370.

117 Id. at 1374.

118 Id. at 1380.

119 Id. at 1382-1384.

120 Recombinant DNA techniques include sequencing and synthesizing a specific gene that encodes for a particular protein, inserting this gene into a special plasmid called an expression vector, and then introducing the vector into a bacterium, yeast, or mammalian cell where the inserted gene directs the synthesis of its encoded protein. See ALBERTS, supra note 51, at 193.

Stanley N. Cohen and Herbert W. Boyer were the first to report that a gene could be cut from the genome of a donor organism, recombined *in vitro* with DNA of a host organism, and re-introduced into cells of the host, thereby conferring the gene's characteristic function to the host. See Cohen & Boyer, *Construction of Biologically Functional Bacterial Plasmids in Vitro*, 70 PROC. NATL. ACAD. SCI. 3240 (1973).

Cohen & Boyer received the following patents for the "biologically functional molecular chimeras": U.S. Patent No. 4,237,224; U.S. Patent No. 4,468,464; and U.S. Patent No. 4,740,470.

121 853 F.2d 894 (Fed. Cir. 1988).

122 Id. at 899.
published experiments.\textsuperscript{123} Although the reference had suggested that the method might be used to make proteins, the patent applicants argued that uncertainty in the field of recombinant technology made this substitution merely "obvious to try" and not obvious for the purpose of §103.\textsuperscript{124} The court declared that obviousness does not require "absolute predictability of success" but only a "reasonable expectation" thereof.\textsuperscript{125}

Furthermore, the court explained that inventions that are "obvious to try" could be patentable if there were other mitigating factors, including: 1) no reasonable expectation of success; 2) a requirement for undue experimentation which involved varying all parameters until one could arrive at a successful result, where the prior art gave no indication of which parameters were critical; or 3) the work was an exploration of a new technology that "seemed to be a promising field of experimentation, where the prior art gave only general guidance as to how to achieve the claimed invention."\textsuperscript{126} Since these indicators of non-obviousness were not present in the O'Farrell application, the court affirmed the examiner's rejection.\textsuperscript{127}

In Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., the Federal Circuit upheld the validity under 35 U.S.C. §103 of Amgen's product claim to a purified gene for erythropoietin.\textsuperscript{128} Because the prior art did not suggest that the probing strategy used by Amgen to isolate the gene would be likely to succeed, the court agreed that the claimed gene itself was non-obvious.\textsuperscript{129} Under this analysis, an inventor may be able to satisfy the non-obviousness requirement for patenting a previously unavailable DNA sequence by showing that the techniques he used to obtain the gene are themselves new and non-obvious.\textsuperscript{130} This analysis conflicts with the long-established principle that one cannot obtain a patent on an old product simply by developing a non-obvious way of obtaining that product.\textsuperscript{131} However, it is consistent with other cases in which patents on products that were obviously desirable, but unobtainable by then-existing methods have been granted to inventors who developed non-obvious means of making these products.\textsuperscript{132}

\textsuperscript{123} Id. at 900-901.
\textsuperscript{124} Id. at 902.
\textsuperscript{125} Id. at 903-904.
\textsuperscript{126} Id. at 902-903.
\textsuperscript{127} In fact, the court found that the cited reference provided evidence that the substitution taught by the claimed invention had a reasonable chance of success. Id. at 904.
\textsuperscript{129} Id. at 1208.
\textsuperscript{130} Rebecca S. Eisenberg, Patenting the Human Genome, 39 EMORY L. J. 721, 736 (1990).
\textsuperscript{131} Buono v. Yankee Maid Dress Corp., 77 F. 2d 274, 279 (2d. Cir. 1935).
\textsuperscript{132} See, e.g. In re Irani, 427 F. 2d 806 (C.C.P.A. 1970) (reversing rejection of patent on crystalline ATMP on ground that it would not have been obvious how to make such a product under the prior art); Shaw v. E.B. & A.C. Whiting Co., 417 F. 2d 1097 (2d. Cir. 1969), cert. denied, 397 U.S. 1076 (1970) (upholding validity of product patent on artificial filaments with cruciform shape and linear orientation of molecules on ground that it was not obvious in the prior art how to make such a product.)
In the present case, the PTO rejected several of NIH's claims under §103.13. The patent examiner found two prior art references that taught the use of DNA fragments as probes for identifying genes. In addition, the examiner found a published DNA sequence that contained a segment corresponding to one of those disclosed by NIH. The examiner noted that these references could be combined to make NIH's invention obvious to one of ordinary skill in the art.

Enabling Disclosure: §112.

The *quid pro quo* for obtaining a patent is an adequate disclosure of the claimed invention. The rules regarding adequacy of disclosure in a patent specification are found in the first paragraph of 35 U.S.C. §112 (1988). These rules ensure that an inventor had possession of the claimed invention on the filing date of the application. They also ensure that the specification provides a sufficient teaching so that one of skill in the pertinent art can make and use the claimed invention. This is referred to as the enablement requirement.

In *In re Fisher*, the Court of Customs and Patent Appeals (C.C.P.A.) stated that "the scope of the claim[ed invention] must bear a reasonable correlation to the scope of enablement provided by the specification." Because biotechnology inventions are often claimed broadly, the enablement requirement poses special problems for biotechnology patent applications. This is well-illustrated in *Amgen, Inc. v. Chugai Pharmaceutical, Co.*, where the plaintiff not only tried to claim the forms of human recombinant erythropoietin that it had made, 

135 Id. at 15-20.
138 The first paragraph of 35 U.S.C. §112 (1988) reads as follows:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.


The second paragraph is directed to the claims. The claims define the legal boundaries of the patented invention. *In re Anderson*, 471 F. 2d 1237, 1241 (C.C.P.A. 1973). If the claims are ambiguous, the court will interpret them in light of the specification. *Aktiebolaget Karlstads Mekaniska Werkstad v. United States Int'l Trade Com'n*, 705 F. 2d 1565, 1576 (Fed. Cir. 1983).
140 *In re Moore*, 439 F. 2d 1232, 1236 (C.C.P.A. 1971).
141 Id.
but also all analogs\textsuperscript{145} that could be made in the future. The court noted that the gene encoding EPO contained about 4000 nucleotide bases\textsuperscript{146} and that Amgen had only disclosed how to make EPO and a few analogs.\textsuperscript{147} Applying the rule of \textit{Fisher}, the Federal Circuit found that Amgen's specification was insufficient to support a claim to all possible analogs of EPO and upheld the lower court's conclusion that the generic DNA sequence claims were invalid under §112.\textsuperscript{148}

The specification need not teach and preferably omits what is already well known in the art.\textsuperscript{149} However, it still must provide sufficient detail to enable the skilled artisan to practice the invention without undue experimentation.\textsuperscript{150} Some experimentation is acceptable as long as it is not undue.\textsuperscript{151} In \textit{In re Forman}, the Board of Patent Appeals set forth the following factors for determining what constitutes undue experimentation: 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented in the application; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims.\textsuperscript{152} Since these factors are illustrative and not mandatory, it is not necessary for the examiner or court to use all of them in determining whether a specification fulfills the requirements of §112.

In the present matter, NIH initially claimed not only the 315 partial gene fragments sequenced by Dr. Venter, but also the whole genes encompassing the fragments,\textsuperscript{153} the proteins encoded by those genes,\textsuperscript{154} and antibodies to these proteins.\textsuperscript{155} In its continuing application of July, 1992, NIH dropped the claims to the proteins and antibodies but retained the claims to the full genes.\textsuperscript{156} The NIH proposal provides a general description of how to use these fragments to find the full-length gene and how to achieve expression of the gene once it is found,\textsuperscript{157} but the disclosure is not detailed.\textsuperscript{158} The examiner noted that NIH admitted the

\begin{itemize}
  \item An analog of EPO is a protein that exhibits one or more of the biological properties of EPO despite some substitutions in the amino acid sequence of the molecule. \textit{Id.} at 1212.
  \item Since 3 nucleotide bases in a DNA sequence encode one amino acid, the protein encoded by this sequence should contain approximately 1330 amino acid. \textit{See} ALBERTS, \textit{supra} note 51, at 102. The district court had found that over 3,600 analogs could be made by substitution at only a single amino acid position on this protein. \textit{Amgen}, 927 F. 2d at 1212.
  \item In \textit{In re Moore}, 439 F. 2d 1232, 1236 (C.C.P.A. 1971).
  \item In \textit{In re Wands}, 858 F. 2d 731 (Fed. Cir. 1988).
  \item In \textit{In re Wands}, 858 F. 2d 731 (Fed. Cir. 1988).
  \item Venter Application, Claims 6, 7 & 8.
  \item Venter Application, Claim 13.
  \item Venter Application, Claim 14.
  \item \textit{See} Eisenberg, \textit{supra} note 14, at 904.
  \item Venter Application, at 3-4.
  \item \textit{See} Eisenberg, \textit{supra} note 14, at 905.
\end{itemize}
possibility of errors in the sequence data. Thus, the disclosure could not be relied upon by one of skill in the art to produce the claimed invention. In addition, the examiner found that several of the claims required some knowledge about the coding regions of the DNA's and that the application gave no information regarding these regions. Because the specification offered no guidance as how to isolate or identify all of the sequences claimed, undue experimentation would be required to produce these sequences and their products. Thus, the examiner objected to the specification under 35 U.S.C. §112 for failing to provide an enabling disclosure.

POLICY CONSIDERATIONS IN SUPPORT OF NIH'S PATENT APPLICATION

Considering the numerous objections of the PTO to NIH's application and predictions that the application would fail, one might wonder why NIH sought patent protection at this early stage of its research on the human genome. NIH reasons that such patents are necessary 1) to promote use of this knowledge for subsequent development of products to diagnose and treat genetic diseases and 2) to protect the U.S. biotechnology effort. NIH's decision is consistent with government policy toward patenting of government-funded research. It also recognizes the problems that the biotechnology industry has with current patent law doctrines.

Government Policy Regarding Federally-Funded Research: Technology Transfer

Dr. Venter's federally-funded research at the NIH was part of the Human Genome Project, an international effort begun in 1986 to sequence, identify and map all of the human genes. The decision of the United States Government to
join in this project was based upon recommendations which it received from the National Research Council of the National Academy of Sciences and the congressional Office of Technology Assessment (OTA). The OTA, especially, was concerned that the large federal investment in the project be translated into new products and services beneficial to U.S. citizens. To promote commercial development of genome research, the OTA recommended that project investigators seek patents on their discoveries. The patentee then could grant an exclusive license to a private investor to induce him to develop the invention into a product that is useful to the public. This is referred to as technology transfer. Proponents of technology transfer contend that this process leads not only to new projects but also to new jobs.

The OTA also expressed its concern that a U.S. inventor could lose control of a federally-funded invention if he did not file a patent for it and a foreign inventor who independently made the same discovery did. A possible consequence of this would be that the foreign patentee would not give manufacturing preference to U.S. firms. In addition, the U.S. inventor would be prevented from use of the invention. Thus, OTA recommended that investigators on the genome project, such as Dr. Venter, seek patents on their inventions.

Current statutory law designed to promote technology transfer provides another compelling reason for NIH's action. Under 15 U.S.C. §3713, a federal agency that refrains from patenting or otherwise promoting commercialization of an employee's invention must allow the employee to retain title to the invention. Had NIH not sought a patent for his work, Dr. Venter might have been able to obtain the patent for himself. The result would be that a single private individual would have patent rights to an invention that had been funded at considerable expense by U.S. taxpayers.

and genes, function of identified genes, and other related information; 2) to create maps of human chromosomes that would permit scientists to locate genes quickly; 3) to create repositories of research materials; 4) to develop new instruments for analyzing DNA; 5) to develop similar resources for other organisms that would facilitate biomedical research and 6) to determine the DNA sequence of a large fraction of the human genome and that of other organisms. Id. at 7.

Victor A. McKusick, Mapping and Sequencing the Human Genome. 320 NEW. ENG. J. MED. 910 (1989).


See Mapping Our Genes, supra note 168, at 168.
See Kiley, supra note 14, at 915.
See Mapping Our Genes, supra note 168, at 165.
See Kiley, supra note 14, at 915.
See Mapping Our Genes, supra note 168, at 168.
Id.
Id.

15 U.S.C. §3710(d) (1988). Normally, a government employee assigns all patent rights to inventions made in the course of his employment to the government. This statute allows him to regain those rights if the government does not pursue the patent.

Dr. Venter has left NIH to head a new non-profit biotechnology institute. Robin Herman, NIH Genes Researcher is Leaving For His Own Lab, WASH. POST, July 7, 1992, at Z4.
Need for Patent Protection for Biotechnology.

Analysts project that U.S. sales of biotechnology-derived products will reach $40 billion by the year 2000 and that world-wide sales will reach $100 billion. As expected, international competition in this potentially-lucrative industry is increasing. Currently, U.S. biotechnology companies appear to be ahead of their foreign competition in most respects, but this might not always be the case. Many commentators have suggested that patent rights are crucial for this U.S. industry, especially while it is in its infancy. Because the initial investments and the risks involved in new product development in biotechnology are quite high, these commentators argue that under-investment will occur unless this industry is given added protection through patenting. In addition, U.S. companies may face stiff foreign competition from imported products based on U.S. inventions unless these inventions are given patent protection. These types of arguments may have provided some of the impetus for NIH's decision to file its patent application on Dr. Venter's discoveries.

Uncertainty in Patenting Biotechnology Products and Processes

The Supreme Court decision in Diamond v. Chakrabarty, which held that a living, man-made microorganism is patentable, opened up the floodgates on patent applications for biotechnology products and processes. However, uncertainty regarding the patentability of these biotechnology inventions is great because the techniques are new and complex and because there is comparatively little case law interpreting the criteria for granting these patents. Consequently, most of the PTO's decisions have been based on case law regarding chemical or pharmaceutical inventions. However, such inventions may not analogize well to biotechnology discoveries.

180 Biotechnology products include DNA sequences, recombinant DNA, monoclonal and polyclonal antibodies, peptides, pharmaceuticals, vaccines, enzymes, cell lines, diagnostic kits, processes for synthesizing or obtaining these materials, diagnostic processes, treatment processes and related instrumentation. See Ihnen, supra note 61, at 407.
183 See id.
184 For a description of biotechnology as an industry which is relatively new, small, and exceptionally sensitive to any perturbation in its economic environment, see Burk, supra note 27, at 16-21.
186 See Burk, supra note 27, at 22-23.
187 U.S. laws prohibit importation for sale of a patented product manufactured in a foreign country unless the patentee has given the foreign company a license to make the product. 35 U.S.C. §271 (a) (1988).
188 See Ihnen, supra note 61, at 407.
189 See Mapping Our Genes, supra note 168, at 167.
190 See Adler, supra note 62, at 909. For a discussion of how In re Durden, 763 F. 2d 1406 (Fed. Cir. 1985), a chemical case, has been misapplied to biotechnology-derived process claims, see Beier & Benson, supra note
Three patent doctrinal requirements have presented unique problems to the patentability of biotechnology inventions: utility,\(^{191}\) obviousness, and enablement.\(^{192}\) Of these, obviousness has proven to be the most troublesome.\(^{193}\) One commentator has noted that the 1986 *Hybritech* decision\(^{194}\) and the 1988 decision in *O'Farrell*\(^{195}\) regarding obviousness of biotechnology inventions focus on different considerations and, therefore, do not provide a clear standard for determining obviousness.\(^{196}\) Another unusual basis for finding non-obviousness is put forth in *Amgen*, in which the claim for a DNA sequence for a human gene was found non-obvious because the procedures used to isolate the gene were non-obvious.\(^{197}\) This appears to confuse the patentability of the product with the non-obviousness of the process used to obtain it.

Although *Amgen* lowers the non-obviousness hurdle somewhat, a patent examiner could still reject many biotechnology patent applications because the processes for making new biotechnology products tend to be well-known and their use widespread.\(^{198}\) The rapid transition that occurred in the patentability of monoclonal antibodies provides a good example of this. In *Ex Parte Old*, the Board of Patent Appeals and Interferences (Board) reversed the examiner's rejection under 35 U.S.C. §103 of claims to monoclonal antibodies for cell surface antigens of human renal cancer because the technology used was an empirical art in which the results were unpredictable.\(^{199}\) Thus, the results were unexpected and non-obvious.\(^{200}\) One year later, in *Ex Parte Erlich*, the Board affirmed rejection under 35 U.S.c.§103 of claims to monoclonal antibodies for fibroblast interferon.\(^{201}\) It found that once the antigen is selected, the use of the antigen in the known method would allow one to approach this project with a reasonable expectation of success.\(^{202}\) Although the steps required to obtain this product were "tedious and laborious," the Board found they were routine in the field and, therefore, did not render the product non-obvious.\(^{203}\) Because of the rapid advances in

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182 at 176-181. For a discussion of how previous decisions regarding product-by-process claims have a negative impact on biotechnology patent applications see Burk, *supra* note 27, at 34-40.
191 See *Kelly*, *supra* note 65, at 273.
192 See *supra* text accompanying notes 136-141.
193 For a discussion of how the utility requirement impacts on biotechnology, see *Kelly*, *supra* note 65, at 277-281.
194 See *supra* text accompanying notes 113-119.
195 See *supra* text accompanying notes 121-127.
196 The invention in *Hybritech* was obvious to try, and none of the mitigating factors enumerated in *O'Farrell* were present in *Hybritech*. Nevertheless, the invention in Hybritech was found nonobvious. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1381 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). This suggests that the Federal Circuit used different criteria in deciding the two cases. See Murashige, *supra* note 112, at 297.
198 See *Kelly*, *supra* note 65, at 280.
200 *Id.*
202 *Id.*
203 *Id.* at 1016.
biotechnology, the law regarding the patentability of DNA sequences is undergoing a similar transition.\(^{204}\)

In the instant case, NIH argues that as soon as it disclosed the partial sequences discovered by Venter, any subsequent products or remaining development steps may have become obvious and therefore unpatentable.\(^{205}\) NIH's arguments is that a molecular biologist of ordinary skill would find sufficient direction in the pertinent art available in 1992 to use these gene fragments to find the complete genes and to use the genes to produce valuable proteins via recombinant DNA technology.\(^{206}\) In response to this claim of obviousness, subsequent inventors could use the criteria of O'Farrel\(^{207}\) to argue that their inventions remained non-obvious because NIH did not provide any information as to the function of these complete genes and, therefore, offered no incentive or direction for searching for a particular gene or protein.\(^{208}\)

NIH's argument is weakened by the examiner's rejection under §112 of its specification due to the lack of an enabling disclosure.\(^{209}\) However, in view of the uncertainty regarding non-obviousness of biotechnological inventions, the PTO's rejection does not necessarily destroy NIH's argument. The specification could well prove revealing enough to render any subsequent invention obvious even though it does not provide enough detail to satisfy the enablement requirement.\(^{210}\) In addition, other scientific advances which cure these enabling deficiencies might occur in the near future. These advances in conjunction with NIH's disclosure could preclude subsequent inventors who discover the useful genes and products related to these sequences from obtaining a patent.\(^{211}\) In fact, many commentators, including those who argue against issuance of a patent for this application, agree that NIH's assessment of the problem for subsequent inventors may be correct.\(^{212}\)

**OPPOSITION TO NIH'S APPLICATION**

NIH's patent application has generated an international debate among scientists, legal experts, and government officials.\(^{213}\) Those who disapprove of

\(^{204}\) See Adler, supra note 62, at 910.

\(^{205}\) See id. Rapid and widespread disclosure of new scientific discoveries is one of the tenants of basic research institutes.

\(^{206}\) See Eisenberg, supra note 14, at 907.

\(^{207}\) See supra text accompanying note 126 for a discussion on how obviousness is determined by the predictability and difficulty of the research needed to obtain these results.

\(^{208}\) See Eisenberg, supra note 14, at 907.

\(^{209}\) See Office Report, supra note 15, at 210 and supra text accompanying notes 160-163.

\(^{210}\) See Eisenberg, supra note 14, at 907.

\(^{211}\) See id.

\(^{212}\) See id.

\(^{213}\) International scientists, legal experts, and government officials debated this issue at a public forum held last May by the Genome Patent Group. Patents, Senate Subcommittee Hearing Focuses on Rejection of NIH Gene Patent Requests, BNA DAILY REPORT FOR EXECUTIVES, September 24, 1992, at 186 [hereinafter...
NIH's action do so either because they think it will not accomplish NIH's goals or because they find it unethical and against patent policy.

**Practical Concerns**

NIH argues that patent protection is necessary to promote investment for developing new products based on its discoveries, i.e. innovation.²¹⁴ Some critics think NIH's argument is unfounded.²¹⁵ Currently, there is no clear proof that property rights are necessary to foster investment in new product development.²¹⁶ Being the first to have a new product on the market may provide sufficient economic benefit to promote investment in innovative research.²¹⁷ In addition, companies could obtain their own process patents on a method for using the "obvious" genes even if NIH does not obtain a product patent for these molecules. However, process patents for biotechnology are less common because most biotechnology methods are routine.²¹⁸ In addition, process patents can be difficult to enforce if the final product gives no clue as to how it was made.²¹⁹

Other critics argue that NIH's broad-scope product patent could actually discourage innovation.²²⁰ This is because anyone who uses the gene fragments or complete genes during development without authority from NIH could be held liable for infringement under 35 U.S.C. §251(a).²²¹ Licensing would be one way to mitigate the problem. However, licensing can still delay the discovery of useful products if NIH were to grant exclusive licenses to a limited number of researchers.²²² In contrast, if NIH were to grant multiple licenses to U.S. biotechnology companies, it could achieve both of its goals of encouraging innovation and promoting the U.S. biotechnology industry.

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²¹⁵ Most members of the biotechnology industry have adopted the policy that patents for DNA sequences should only be granted once the entire sequence and the function of these sequences are known. See POSITION PAPER, supra note 2, at 1.
²¹⁶ For a discussion of the economic theories to support this argument, see Eisenberg, supra note 185, at 1036-1046.
²¹⁷ See id. at 1026.
²¹⁸ For a comprehensive discussion of the problem with obviousness in process patents, see Burk, supra note 27, at 42-57.
²¹⁹ See Eisenberg, supra note 130, at 739.
²²⁰ Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839 (1990) explains how granting broad scope patents for inventions at the early stages of development in a science-based technology discourages others from innovation, i.e. putting the existing invention to practical use and thereby creating new products.
²²² For an economic analysis showing that faster development is better, see Merges Nelson, supra note 220, at 878.
However, even if NIH were to grant non-exclusive licenses to all U.S. biotechnology companies, issuance of this broad-scope product patent sets a bad precedent. Other investigators are doing similar research, and at least one private biotechnology company has filed a patent application for DNA sequences of unknown function. However, NIH cannot control the licensing policies of private investigators. Because the U.S. doesn't mandate licensing for private inventors, these investigators can choose not to grant licenses to subsequent innovators. Thus, private investigators could prevent development of valuable products if they too were granted broad-scope patents.

In addition, most companies prefer to have their own patents on new inventions and not exclusive or non-exclusive licenses. Therefore, if the PTO issued a patent to NIH for the numerous genes it is claiming, many companies might be tempted to abandon their current research efforts aimed at product development and join the rush to sequence fragments. Since the average nucleotide sequence disclosed by NIH contains only 300-500 bases and the average gene contains thousands of bases, patent rights to different parts of a single gene could conceivably be held by more than one "inventor." Thus, companies involved in developing biological products could find they would need multiple licenses to continue their work. At some point, paying royalties to multiple patentees could become economically unfeasible, and the companies would be forced to abandon new product development.

Other critics point out that NIH's potential patent fails to provide complete protection to U.S. companies. The most effective protection against infringement by foreign competitors is a patent for a final end product that is sold to consumers. Such patents provide a right to exclude competitors from selling the patented product regardless of how it is made or what it is used for. Patents on starting materials for making an unpatented end product are less effective. This is because such patents do not prevent a competitor from using the patented material overseas to make the unpatented end product and then importing it into the United States. Since genes are used primarily to produce marketable proteins

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223 The provisions for licensing by a government agency are found in 37 C.F.R. §404 (1992).
224 Amgen, a California biotech company has reported that it has also decoded a large number of genes with undetermined functions. See Herman, supra note 214, at 211.
225 The company, Incyte Pharmaceuticals of Palo Alto, California is gearing up to sequence 100,000 sequences per year. See Anderson, supra note 13, at 301.
227 See POSITION PAPER, supra note 2, at 4-5.
228 See Roberts, supra note 6, at 184.
229 See POSITION PAPER, supra note 2, at 4.
230 See Ginsberg, supra note 4, at 22.
for treating genetic deficiencies, patents issued to NIH for entire genes would not prevent this practice. Even less protection would be provided if NIH is limited to protection for the gene fragments only. This is because the gene fragment would be used to obtain the gene, which is a step even earlier in the process of obtaining a protein. In addition, because NIH could obtain patent rights to these genes long before any patented products made from them are ready to be sold, its licensees would not be able to enjoy protection for the full 17 year patent period.

Policy Considerations

A number of scientists and lawyers consider the patenting of human genes, the very essence of life, unethical. These individuals contend that the human genome is a collective property that should be held in common among all humanity. Recognizing the necessity to protect intellectual property rights, these scientists suggest that process patents be granted for the use of these sequences rather than for the sequences themselves. However, most parties to the debate agree that genetic information can be claimed. They object primarily to NIH’s attempt to claim property rights to complete genes without knowing the entire sequence of these genes or their function. By so doing, NIH is subverting the doctrinal requirements for a patent.

In Brenner v. Manson, the Supreme Court interpreted the utility requirement of §101 to indicate that "a patent system must be related to the world of commerce rather than to the realm of philosophy." This language suggests that the function of the utility requirement is to distinguish between basic research, which should stay in the public domain, and applied technology, which may be patented. Those who agree with this view find that the NIH disclosure of par-

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233 Other genes may serve as components of diagnostic kits. As such, they will be end products and obtain complete protection. See Eisenberg, supra note 14, at 906.
234 Steve Bent, a patent attorney, has predicted that the patent will be limited to the fragments. See Roberts, supra note 6, at 185.
235 For a description of the process, see Roberts, supra note 6, at 184.
239 Dr. Victor McCusick, the founder of the international Human Genome Organization, is one of these individuals. Last month scientists at a Human Genome conference in Brazil issued a Declaration of Patenting of Human DNA Sequences which echoes Dr. McCusick’s ideas. See Herman, supra note 214, at Z11.
240 100 or more patents have already been granted for sequences of complete genes. See id.
241 The patents for other gene sequences were granted in conjunction with a specific process or product for which the gene was to be used. See, id.
244 See Kiley, supra, note 14, at 916; Eisenberg, supra note 14, at 905.
tial gene sequences is too far from the realm of commerce to be patentable. To allow a patent to issue for the whole gene when NIH has only provided a minimal utility for the partial sequences would defy the spirit of this requirement.

The enablement requirement ensures that patents are granted only to those who have added to the "public storehouse of knowledge." Since much of the work done by the Venter group utilized an automated sequencer, many would contend it is unworthy of this type of reward. The Industrial Biotechnology Association, whose members collectively represent 80 percent of U.S. investment in technology, has noted that the real work on the way from partial sequence to final product will be done by others. This organization considers it unfair to permit NIH to exercise complete control over a subsequent product when the agency has contributed so little to the development of the product. However, patents are not necessarily granted to those who do a prodigious amount of work. Nor are they limited only to those who have exhibited a flash of genius.

Individuals involved with the international genome project have expressed great concerns regarding NIH's action. They fear that patenting will hamper the free dissemination of information necessary to realize the goals of this project. However, both patent law and scientific norms favor disclosure. It is much more likely that a decision by other genome researchers to patent their discoveries will merely delay disclosure. These researchers might defer publication of their results until they are certain that they have reached the point of patentability of their invention.

Finally, those who oppose NIH's action predict that genome researchers will abandon their current, unique approaches to the problem and join the mad

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245 See, e.g., Kiley, supra, note 14, at 916.
246 See Eisenberg, supra note 14, at 905.
248 Dr. James Watson, the former director of NIH's genome project and Nobel Prize winner for his work elucidating the structure of DNA, was "horrified" that a patent could be granted to work that could be done by "virtually any monkey." See Roberts, supra note 6, at 184. note 6 at 184.
249 IBA estimates that a typical biotechnology company invests more than three hundred person-years in developing a new drug, while NIH has invested less than 20-person minutes in each sequence. See POSITION PAPER, supra note 2, at 4.
250 See, id.
251 Gillman v. Stern, 114 F. 2d 28 (2d Cir. 1940), cert denied. 311 U.S. 718 (1940) (finding that the test of a valuable discovery is the ingenuity needed for the new conception and not the amount of physical readjustment).
253 Although Dr. Venter has submitted his sequences to the international data bank and has freely shared his discoveries with other researchers, NIH's detractors point out that others might not be willing to do so. See Roberts, supra note 6, at 186.
254 For a discussion of the conflicts and compatibility of science and patent law, see, Eisenberg, Proprietary Rights and Norms of Science in Biotechnology Research, 97 YALE L.J. 177 (1987).
255 See Eisenberg, supra note 130, at 741.
scramble to sequence DNA fragments if the NIH patents issue.\textsuperscript{256} At the very least, they predict a disappearance of co-operation in this international effort.\textsuperscript{257}

**Solutions**

*Preserving Patentability of Downstream Products*

NIH filed its application on partial DNA fragments because it was concerned that subsequent products related to these fragments, such as complete DNA sequences and proteins, would be found unpatentable.\textsuperscript{258} Several commentators agree that NIH's interpretation of the current patent law may be correct.\textsuperscript{259} To overcome this problem, they propose judicial or legislative remedies.\textsuperscript{260}

Downstream inventions could be found unpatentable under §§101 & 102 because they are not "new". Once a researcher publishes information on the composition of matter it becomes part of the public domain.\textsuperscript{261} In the U.S., the product does not become new for patent purposes simply because someone finds a new use for it.\textsuperscript{262} In *In re Thuau*, the Court of Customs and Patent Appeals rejected patent claims to metacresol sulfonic acid-aldehyde condensation products as treatments for diseased tissue because the same compound had earlier been known for other purposes.\textsuperscript{263} Thus, a patent examiner could reject the product claim of a downstream researcher who identifies the biological activity of genes encompassing the sequences published by NIH simply because NIH has shown some minimal utility for these partial sequences. In contrast, European countries allow claims to a substance as it is used for a new purpose even though the underlying substance is old.\textsuperscript{264} On the basis of *Thuau*, it is unlikely that U.S. courts will expand the law in this direction.\textsuperscript{265} Therefore, legislative action would be required to allow these downstream inventors the patent protection granted to their European counterparts.\textsuperscript{266} However, this would be an extreme change in U.S. patent law and does not provide the best solution to the problem.

\textsuperscript{256} There have also been warnings that such wholesale patenting could double the cost of obtaining the human genome sequence. See Roberts, *supra* note 6, at 184.
\textsuperscript{258} See Ginsberg, *supra* note 4, at 2-3.
\textsuperscript{259} See Eisenberg, *supra* note 14, at 907; Kiley, *supra* note 14, at 916. At the outset of the genome project the Office of Technology Assessment concluded that the genome project would most likely not raise new issues of patent law. See *Mapping Our Genes*, *supra* note 168, at 16.
\textsuperscript{260} See, e.g., Adler, *supra* note 62, at 910-913.
\textsuperscript{261} See 35 U.S.C. § 102(a)-(b) (1988) listing publications as prior art.
\textsuperscript{262} *In re Thuau*, 135 F. 2d 344 (C.C.P.A. 1943).
\textsuperscript{263} Id. at 346-47.
\textsuperscript{264} See Kiley, *supra* note 14, at 916.
\textsuperscript{265} Id.
\textsuperscript{266} Id.
At present, it is uncertain whether publication of sequence data would render downstream discoveries obvious. Much depends on how quickly biotechnology advances, how the PTO construes the 1992 level of technological skill, and how the PTO applies previous decisions of the Federal Circuit concerning chemical patents to biotechnology applications. In *In re Dillon*, the Federal Circuit sitting *en banc* held that similarities in structure between a new chemical compound and prior art leads to a *prima facie* case of obviousness. The court held that the discovery of unpredictable properties or functions were not to be considered for determining non-obviousness. Since the genetic code allows one to determine the sequence of amino acids in a protein from the sequences of bases in the corresponding gene, an examiner could use *Dillon* to reject a protein patent application under §103 if the DNA sequence has been disclosed. However, in contrast to chemistry where structure predicts function, biotechnology has not reached the point where the biological function of a protein can be predicted from its primary structure, i.e. sequence of amino acids. Although this would argue against using *Dillon* to reject biotechnology applications, it is too early to tell whether the PTO would accept this argument. To avoid problems of obviousness for inventions flowing from NIH's disclosure, Congress could amend the patent law to declare that publication of partial sequences does not make these subsequent inventions obvious.

As an alternative to amending the patent system, Congress could create a new system to provide proprietary rights in this data. In the past, Congress has created new intellectual property systems to protect novel plant varieties and semiconductor chip masks.

*Preventing Patenting of Partial DNA Sequences by Other Investigators*

NIH has characterized the filing of is application as an interim policy, suggesting that it might decide not to pursue patent rights for partial DNA sequences. However, even if NIH abandons its application, current regulations of

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267 See Greenlee, *supra* note 71, at 132-133.
268 Tertiary structure, or the configuration a given sequence of amino acids acquires upon folding, controls the functionality of a protein. At present, models of protein structure are not sufficiently developed to predict tertiary structure on the basis of sequence information alone. See Greenlee, *supra* note 71, at 136 n. 48.
270 Dr. Venter has proposed an amendment to §103 as follows. "Prior art shall not preclude patentability of an amino acid or nucleotide sequence solely because such prior art discloses a portion of such sequence." *See Subcomittee Hearing, supra* note 213, at 188.
271 See Adler, *supra* note 62, at 913.
274 See Ginsberg, *supra* note 4, at 19. NIH had to file before Venter published his results or forfeit its right to obtain a foreign patent.
the Department of Health and Human Services require that it allow employees such as Dr. Venter to seek patents for themselves. Two measures could fill this loophole. The first suggested approach is a change in the federal law to ensure that federal agencies can prohibit patents on inventions made by their employees if the agency, after due process, determines such patents are not in the public interest. The second is that NIH seek an advisory opinion from the Justice Department to the effect that publication alone would constitute commercialization under the Federal Technology Transfer Act. This would foreclose NIH employees or extramural researchers funded by NIH from obtaining patent rights under 15 U.S.C. §3710d for such inventions.

In the alternative, NIH could seek an international agreement that all governments and their research grantees involved in the human genome project will not seek patents on DNA's of unknown biological activity. Many foreign countries have already indicated that they support this policy. However, such an agreement would still allow those in the private sector to obtain patents having no greater basis than that disclosed by NIH. To prevent this possibility, it might be necessary to redefine utility and set a higher threshold for this requirement. Despite language in Brenner v. Manson that the utility must be "substantial", only a minimal showing of utility has been required in many recent court decisions. In contrast, the British require an invention be capable of industrial application. However, withholding patents on early research discoveries with a minimal utility could prevent early disclosure and cause researchers to protect their discoveries as trade secrets. Consequently, this might not be the best approach from a public policy standpoint.

275 See supra text accompanying notes 181-183.
276 Dr. Venter's remarks suggest that he is not interested in obtaining gene patents for himself. See, e.g. Herman, supra note 179, at 24; Subcommittee Hearing, supra note 213, at 186. However, similar problems that arise in the future could be prevented by taking the proposed actions now.
277 See Kiley supra note 14, at 918.
278 See Position Paper, supra note 2, at 6.
279 See Kiley, supra note 14, at 917.
280 In response to NIH's move, the United Kingdom also filed patent applications for gene fragments. The French handed over their research results to UNESCO as a symbolic protest against the American and British attempts to obtain these patents. Over 200 scientists from around the world also signed a declaration sent to UNESCO calling for the results of the genome project to remain in the public domain. Declan Butler, Who Owns the Building Blocks of Life?, THE INDEPENDENT, Nov. 2, 1992, at 14. At the same time the U.K. government filed its application, it announced its intention to seek an international agreement disallowing patents for gene sequences of unknown utility. Alan Howarth, Letters, 256 SCIENCE 11 (1992).
281 For an explanation as to how NIH could obtain judicial review of this issue in the Supreme Court and why it might not be possible, see Kiley, supra note 14, at 917.
282 See, e.g., E.I. DuPont de Nemours & Co. v. Berkley & Co., 620 F. 2d 1247 (8th Cir. 1980) (stating that a commercially successful product is not required.); Envirotech Corp. v. Al George, Inc., 730 F. 2d 753 (Fed. Cir. 1984) (finding that an invention which has limited utility and is only operable in certain application should not be rejected for lack of utility).
283 See Kiley, supra note 14, at 917.
284 See Eisenberg, supra note 14, at 905.
Another proposed solution with broad implications is a moratorium on issuance of all patents for "human tissue, fluid, cell, gene, or gene sequences." This would prevent researchers from obtaining patent rights on partial sequences and allow time for debating the issues presented by such applications. However, it also could destroy the U.S.'s lead in biotechnology.

Promoting Innovation

If the NIH patents were to issue, this agency could prevent others from using the fragments to find genes and from using the genes to produce proteins. To prevent a limited number of individuals from having complete control over subsequent research utilizing these fragments and/or genes, commentators have suggested that NIH grant non-exclusive licenses to all-comers or dedicate them to the public. Again, this solution would have no impact on a private sector researcher who obtains similar broad-scope patents.

To prevent such private sector patentees from impeding subsequent research, some commentators have suggested a legislative experimental use exception to 35 U.S.C. §271(a), which gives the patent-holder the power to enjoin an infringer. Although an exception for experimental use has been implied to this statute, the Federal Circuit held the exception to be "truly narrow" in its most recent ruling on this issue. Thus, it is not necessary for the plaintiff to suffer monetary damages before the defendant is found liable. In addition, an 'innocent' infringer can be held liable. Because the exception is not applicable unless the use is for amusement, to satisfy idle curiosity or for strictly philosophical inquiry," it is of no value to commercial corporations, whose charters normally do not authorize such activities. Because the lines between academic research and commercial research are blurred in the area of biotechnology, the defense may not be available to researchers at non-profit institutions.

285 The moratorium was proposed by Senator Mark Hatfield (R-Ore) in an amendment to the NIH Reauthorization Act of 1991. See Slind-flor, supra note 242, at 39.
286 The moratorium was opposed by Dr. Sullivan, the secretary of the Department of Health and Human Services under President George Bush. See id.
287 See Ginsberg, supra note 4, at 42.
288 35 U.S.C. §271(a) (1988) reads as follows: Except as otherwise provided in this title, whoever without authority makes, uses, or sells any patented invention, within the United States during the term of the patent therefor, infringes the patent.
290 Id. at 861.
292 Roche, 733 F. 2d at 863.
294 See Eisenberg, supra note 185, at 1017-18 which discusses the overlap between basic and applied research.
non-profit organizations are rarely sued for infringement, it has happened on occasion.

An expanded experimental use defense is especially important when the claimed invention is a basic research tool, as it is in the present case. Free access to these early discoveries is necessary for optimum development of new and improved products. However, an overly-broad exception could reduce the strength of patents to the point where they do not provide an incentive to invent. Thus, the exception must be appropriately drafted to satisfy the competing objections of the patent system: incentive to invent and benefit to the public. Two sets of recommendations have been proposed for a new statutory experimental use exception. Both recognize that a researcher and potential competitor should not be enjoined from using a patented basic research tool if that use results in the improvement of the tool or development of a new product. Rather, such use should require payment of a reasonable royalty to the initial inventor if the product becomes commercially profitable. This type of exception provides certainty for the competitor and thus encourages investment in biotechnological research. It also allows both the initial inventor and the innovator to reap appropriate rewards from their contributions and benefits the public by production of new and useful products.

Since the number of competing products and processes that will infringe upon a patent is directly proportional to its scope, another means of protecting subsequent innovators from liability for infringement is to limit the scope of these patents. Critics of broad-scope product patents at the early stages of product development contend that awarding limited patents is also more consistent with the enablement doctrine of § 112. In the present case, limiting patent protection to the fragments only could reduce the number of cases of literal infringement.

As one commentator suggested, the blocking power of these product patents can be limited further if the courts apply the Doctrine of Reverse Equivalents to

See Feit, supra note 293, at 822. Possible explanations for failure of patentees to sue non-profit research institutions include: lack of knowledge about the infringement and a realization that research efforts by non-profit organizations which improve or provide a new use for the product may make the original product more valuable commercially. See, Eisenberg, supra note 130, at 741.


For a discussion of the importance of free access see Eisenberg, supra note 185, at 1046-1066.

See id., at 1033-34.

See Feit, supra note 293, at 839-840.

See id., at 840 Eisenberg, supra note 185, at 1078.

See Feit, supra note 293, at 840-41.

Id. Surprisingly, members of the biotechnology industry have indicated they see no need for such an exception. See Adler, supra note 220, at 839.

See Merges & Nelson, supra note 220, at 839.

Id. at 915.
accused infringers who use the encompassing genes in recombinant protein production. This defense is allowed to the accused infringer when his product is "so far changed in principle" from the claimed product that it "performs in a substantially different way and is not therefore an appropriation." The Federal Circuit has stated that the purpose behind the doctrine is to "prevent unwarranted extension of the claims beyond a fair scope of the patentee's invention." When applying the doctrine, the court is to weigh the accused devise against the equitable scope of the claims, which in turn is determined in light of the specification, the prosecution history and the prior art. Since the NIH application discloses a use of the gene fragment for obtaining a complete gene and provides only general instructions for subsequent development, this commentator contends that use of the implicated gene to direct synthesis of a protein can be excused under the doctrine because the use falls outside the equitable scope of the claimed invention.

Because the doctrine is applied only in cases of literal infringement, the accused infringer's improvement must be significant to qualify for this immunity. If courts were to excuse literal infringement often, the faith of inventors in the patent system would diminish. Since some courts may not find recombinant protein production a significant improvement over NIH's claimed invention, they may not be willing to apply a doctrine which conceivably has a negative impact on the patent system. In fact, successful use of the doctrine is fairly rare.

CONCLUSION

Some individuals consider patenting human genes unethical. Nonetheless, the courts have upheld product patents issued to researchers who have determined the complete sequence and biological function of the claimed gene. Recently, NIH filed an application claiming patent rights to thousands of human genes even though it had sequenced only a segment of the genes and had no idea of their biological functions. NIH has given several reasons for its unusual actions. First, the agency contends that patent protection for these genes is neces-

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306 See Greenfield, supra note 21, at 1095.
307 SRI Int'l v. Matsushita Elec. Corp. of America, 775 F. 2d 1107, 1107 (Fed. Cir. 1985) (en banc).
309 The prosecution history found in the records of the patent office can be used like legislative history to assist in the construction of the claims that survive in the issued patent. See 4 DONALD S. CHISUM, PATENTS §18.05 (1992). If a patentee agrees to certain limitations of the claims as required by the patent office, he cannot sue for infringement of the unlimited invention. Graham v. John Deere Co., 383 U.S. 1, 33-34 (1966).
310 Scripps, 927 F.2d. at 1581 (emphasis added).
311 See Greenfield, supra note 21, at 1082.
312 See Merges & Nelson, supra note 220, at 867 n. 120.
314 See Herman, supra note 214, at Z11.
315 See Leary, supra note 7, at B26. It is expected to take the PTO a year to issue its final ruling on NIH's application. See Anderson, supra note 13, at 302.
sary to encourage development of related biomedical products. This is consistent with federal policy regarding technology transfer of government-funded research. Considering the opposition from the biotechnology industry to issuance of these patents and the lack of economic data supporting this policy, NIH's first premise is at best debatable.

NIH also contends that publication of the partial sequences could preclude subsequent researchers who develop related products from obtaining patent protection for their inventions. A number of legal experts who consider this prediction possible have suggested alternative solutions to this potential problem. The problem could be avoided if Congress were to declare that disclosure of partial gene sequences does not render subsequent related discoveries obvious. Because this proposed change is so specific, it would have less impact on the whole of patent law than other proposed solutions. In addition, there is precedent which would allow Congress to narrowly-tailor an exception. However, this narrow exception might not solve all the patent problems for potential innovators. Conversely, NIH's prediction of problems for downstream inventors may simply be incorrect.

NIH's application has uncovered problems with 15 U.S.C. §3713, which allows federal employees to retain title to their inventions if the government refrains from patenting or otherwise promoting commercialization of the invention. Under this statute, it is uncertain whether government employees can be prevented from seeking patents on inventions that should be left in the public domain. Recommendations for dealing with this problem include amending the statute or seeking a ruling from the Attorney General which declares that publication constitutes commercialization for purposes of the statute.

NIH's application has also focused attention on other unresolved areas of patent law. For example, the threshold for meeting the utility requirement may be too low to preclude private inventors from obtaining patent protection prematurely. The utility requirement could be strengthened by the judiciary or the legislature. However, if this hurdle is set too high, basic researchers might be tempted to withhold their data until they are certain their products are patentable.

316 See Eisenberg, supra note 14, at 904.
317 See supra text accompanying notes 169-175.
318 See Roberts, supra note 6, at 185.
319 See supra note 270.
321 See POSITION PAPER, supra note 2, at 6.
Before policy makers alter the law to preclude patenting of basic research, they should consider other consequences. In the past, basic research at non-profit institutions was funded almost exclusively by the government. However, because the national debt is so high, scientists can no longer presume that sufficient government funding for all basic research will continue in the future. The patent system provides an alternative for funding scientific research. If it were no longer available to basic researchers, the growth of scientific knowledge could be retarded.

Other solutions have been proposed to minimize the negative legal impact of patenting basic research tools on subsequent innovators. These include limiting the scope of the patents or expanding the experimental use exception. Such solutions provide viable alternatives to the problem and are less likely to produce adverse consequences for basic research than strengthening the utility requirement.

Although the judiciary could clarify some of these issues, it is not capable of resolving all of them. In addition, judicial review is time-consuming and is not easily directed at a particular problem. Because some of these problems may require a policy change, Congress is the most appropriate governmental body to remedy the situation. Hopefully, after considered debate, it will change patent law in a manner which protects the biotechnology industry without undermining the Constitutional policies that form the basis for the patent system.

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322 See Eliot Marshal & David P. Hamilton, R & D Budget Collides with the Deficit. 258 SCIENCE 208 (1992) for a report on federal budget cuts for basic research.
323 See generally Merges & Nelson, supra note 220.
324 See, e.g., Eisenberg, supra note 186, Feit, supra note 293.
325 At the request of Senator Edward Kennedy (D-Mass) the Office of Technology Assessment launched a study on the propriety of gene patents and their impact on research. If Congress decides to enact legislation on the issue, it should have the results of the study by April, 1994. See Anderson, supra note 13, at 302.
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