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Comment

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by Robert S. Schwartz*

I. Introduction

The pioneering case of *Diamond v. Chakrabarty*[1] broadly construed the utility requirement of the patent statutes[2] and established that "anything under the sun that is made by man" is patentable.[3] This holding, *inter alia*, opened the door to the patentability of genetic material (genes and related polynucleotides)[4] and products based on the exploitation of genes,[5] and fa-

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1. Diamond v. Chakrabarty, 447 U.S. 303 (1980) (granted patent protection to living, naturally occurring microorganisms because the microorganisms had been altered by human introduction of non-naturally occurring material, causing them to have different properties than their non-manipulated naturally occurring counterparts).

2. The utility requirement of the patent act is codified in 35 U.S.C. § 101 (2003) ("Whoever invents or discovers a new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.").

3. *Chakrabarty*, 447 U.S. at 309.

4. A gene is the physical and functional unit of heredity, which carries information from one generation to the next. It is the entire DNA sequence necessary for production of a functional protein or RNA. All naturally occurring DNA contains four chemical moieties called nucleotide bases; adenine (A), thymine (T), gua-

cilitated the soon to follow biotechnology revolution.[6] Courts were quick to appreciate the unprecedented potential of this biotechnology revolution[7] and were legitimately concerned

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nine (G), and cytosine (C). These four bases are repeated in a particular non-random order in a gene and contain within their specific ordering all the information required for a cell to synthesize a protein unique for that DNA sequence (*See infra* note 5). Genes also contain regions of DNA that do not encode for proteins (introns and non-coding regions) but play other roles such as regulation of the expression of that gene. Structurally, a gene is a double-stranded molecule in which the two DNA strands are oriented in an antiparallel fashion, and the nucleotide bases which comprise each strand hydrogen-bond to those of the opposing strand based on their complementarity. One DNA strand codes for the protein of interest, and is thus referred to as the "coding" or "sense" strand. The opposing, complementary strand is referred to as the "template" or "antisense" strand. *See generally* BENJAMIN LEWIN, 7 GENES 6-9, 119-20 (2000).

5. The products of genes are proteins that are composed of a polymer of interconnecting amino acids encoded for by the DNA of that gene. Proteins are the cellular workhorses and participate in nearly all cellular processes. The human genome comprises approximately 30,000 genes. *See* J.C. Venter et al., *The Sequence of the Human Genome*, 291 SCIENCE 1304, 1305–51 (2001). While DNA typically exists in a double helical structure, proteins exist in more complex structures (the predominate forms being globular, helical and sheeted) that are largely determined by the amino acid composition of the protein. To a large extent it is the three dimensional structure of proteins that confer their physical and functional properties. A protein's spatial structure is now often used to aid in the design of pharmaceuticals. *See generally* MOLECULAR BIOLOGY OF THE CELL 129-44 (Bruce Alberts et al. eds., 4th ed. 2002).

6. It is generally regarded that the biotechnology revolution was started by the combined efforts of venture capitalist Robert A. Swanson and Stanford University Professor Herbert W. Boyer, who founded the world's first biotechnology company Genentech in April 1976. Today Genentech is one of the world's largest biotechnology companies with annual revenues in excess of $2.7 billion. Genentech website, *at* http://www.gene.com/gene/ir/financials/annual-reports/2002/financials.htm (last visited Dec. 3, 2003).

7. Gene-based recombinant protein technology has revolutionized the manner in which proteins are produced. Before recombinant protein technology it was necessary to isolate and purify proteins from natural sources. This was tedious and impractical for low-abundance proteins. *See* MOLECULAR BIOLOGY OF THE CELL, *supra* note 5, at 492-513. This process also had the limitation that only naturally occurring proteins could be produced; modified proteins, which often have beneficial properties compared to their naturally occurring counterparts, could only be produced through post-purification manipulations. In addition, traditional protein purifications were costly. *Id.* The development of recombinant protein technology eliminated the need to isolate and purify proteins from their natural sources. *Id.* Genes, or synthetic DNA, encoding those proteins could be used to direct other cells to synthesize the protein(s) encoded by the inserted DNA. *Id.* The result of recombinant protein technology was that commercial production of proteins was no longer tied to the availability of natural sources. *Id.* For example, prior to recombinant protein technology, insulin, a protein hormone required for glucose metabolism, and which is either defective or produced in insufficient quantities in

about granting too wide a scope of patent protection for gene-based inventions to the first entrants.[8] This was necessary to prevent first entrants from monopolizing the new technology,[9] a result that the courts feared would stifle its development. As will be discussed below, the primary method the courts used to achieve this was to define a gene as a chemical compound and apply analogous patentability standards. The result was that genes were not held to be patentable unless the entire structure (i.e., the entire nucleotide sequence) of the gene was disclosed.[10] However, by focusing on the gene's structure rather than on the properties of the proteins encoded by those genes, the courts did not anticipate that the nucleotide sequence of every gene[11]

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diabetics (resulting in the inability to maintain normal blood "sugar" levels), had to be physically purified from natural sources, usually animal tissue. *See* Regents of Univ. Calif. v. Eli Lilly, 119 F.3d 1559, 1562 (Fed. Cir. 1997). This greatly reduced both the availability of insulin for therapeutic use as well as increasing its cost. *Id.* In addition, purification of proteins from animal tissues has associated risks of co-purification of animal viruses and other pathogens, and since the insulin produced is non-human, it may cause allergic reactions in sensitive individuals. *Id.* Recombinant DNA technology changed that by permitting the production of insulin (and essentially any other protein) in laboratory cell culture, avoiding the necessity of using animal tissues. *Id.* Most importantly, recombinant protein technology allowed the commercial production of human proteins, which, prior to this technology, were often impossible to produce commercially due to the unavailability of large amounts of human tissue needed for protein purification. *Id.* In addition to its clinical utility for human and other animal diseases, recombinant protein technology also has revolutionized agribusiness by allowing for the introduction of new genes (and hence new properties) into crops that has dramatically affected the agricultural industries of the United States and, particularly, third world countries where agriculture remains the primary source of the economy. *See* Margaret R. Grossman, *American Law in a Time of Global Interdependence*, 50 AM. J. COMP. L. 215-17 (2002).

8. *See* Michael D. Davis, *The Patenting of Products of Nature*, 21 RUTGERS COMPUTER & TECH. L.J. 293 (1995).

9. Patent protection gives the inventor the exclusive right to make, use, or sell the patented product for a statutory time period (20 years from the patent application filing date for applications filed on or after June 8, 1995 or 17 years from the date of patent issuance for applications filed before June 8, 1995). *See* 35 U.S.C. § 154 (2003).

10. The courts used primarily the written description requirement set out in 35 U.S.C. § 112 (2003), paragraph 1. The policy behind the written description requirement is to guard "against the inventor's overreaching by insisting that he recount his invention in such detail that his future claims can be determined to be encompassed within his original creation." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561 (Fed Cir. 1991) (citations omitted). *See also infra* Part IV.

11. *See infra* Part II.

would someday be known and publicly available.[12] As this Note will argue, the publication of the human genome[13] will necessarily require a reconsideration of the patentability requirements for gene-based inventions, and, will most likely lead to significant short-term uncertainty concerning the patentability standards for such inventions. This uncertainty likely will result in substantial litigation regarding both the granting of gene-based patents by the United States Patent and Trademark Office (PTO),[14] as well as the validity of subsequently issued patents. This Note will also discuss potential economic ramifications flowing from these patentability uncertainties such as risk avoidance through licensing and academic-commercial collaborations. Ultimately, the publication of the human genome[15] (as well as the genomes from other species),[16] should stimulate the evolution of new legal standards for the patentability of genes and gene-based inventions.

II. Sequencing the Human Genome

In 1990, the United States launched the Human Genome Project (HGP) as a research effort funded largely by the Department of Energy and the National Institutes of Health (NIH). Initially, the HGP had three goals: (1) to identify all of the genes that constitute the human genome;[17] (2) to determine the sequence of the genome's predicted three billion chemical ba-

12. As discussed *infra* Part V, the public availability of a gene's complete nucleotide sequence makes that gene unpatentable by being both anticipated and obvious over the prior art.

13. Venter et al., *supra* note 5, at 1305-51.

14. The organization and responsibilities of the PTO are governed by 35 U.S.C. §§ 1–7 (2003).

15. A "genome" refers to the entire collection of an organism's genes. *See* MOLECULAR BIOLOGY OF THE CELL, *supra* note 5, at G:15.

16. In addition to the human genome, the genomes of mouse, rat, zebrafish, human malaria parasite, fruit-fly, and over one-hundred invertebrate, bacterial and viral genomes have been sequenced as of January 2003. Sequencing projects are also underway for many agriculturally important plant species. *See* http://www.ncbi.nlm.nih.gov (last visited Dec. 3, 2003).

17. The original estimates of anywhere from 100,000 to 50,000 genes in the human genome was reduced to approximately 30,000 after the first draft of the human genome was published. What is remarkable about this number is that it represents only a two-fold increase over the number of genes in a simple organism such as the common roundworm. *See* Venter et al., *supra* note 5, at 1305.

ses;[18] and (3) to license subsequently related technologies to the private sector.[19] However, the efforts of the HGP were soon overshadowed by the introduction into the race of the "startup" genomics company Celera Genomics.[20] The company's C.E.O., J. Craig Venter,[21] claimed Celera would unilaterally sequence the entire human genome in five years or less.[22] Celera and the HGP jointly published, to great fanfare, the first draft of the human genome on February 16, 2001.[23]

III. Obtaining A Patent

Creating property rights in new inventions was considered by our founding fathers to be of such importance to America's development that it was included into the first draft of the United States Constitution.[24] The Constitution grants Congress the power to issue patents "[t]o 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."[25] The *quid pro quo* for the state-sponsored limited monopoly is the requirement that the inventor disclose his invention in such detail as to allow anyone in that field to reproduce it.[26] The public policy rationale underlying this *quid pro quo* is that public disclosure of inventions will benefit development of American society.[27]

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18. The individual nucleotides that comprise DNA are determined by a process called nucleotide "sequencing." *See* MOLECULAR BIOLOGY OF THE CELL, *supra* note 5, at 504-08.

19. *See* The Human Genome Resources, *available at* http://www.ncbi.nlm.nih.gov/genome/seq (last visited Dec. 3, 2003).

20. Celera Genomics (now Celera), *at* http://www.celera.com/index.cfm (last visited Dec. 3, 2003).

21. Dr. Venter stepped down as C.E.O. of Celera Genomics on January 22, 2002. *See* Andrew Pollack, *Scientist Quits the Company He Led in Quest for Genome*, N.Y. TIMES, Jan. 23, 2002, at C1.

22. *See* D. Butler, *Publication of Human Genomes Sparks Fresh Sequence Debate*, 409 NATURE 747, 747-48 (2001).

23. As of April 2003 approximately 100% of the human genome has been sequenced and made available free of charge to the public. NATIONAL HUMAN GENOME RESEARCH INSTITUTE, *at* http://www/genome/gov/11006929 (last visited Dec. 3, 2003).

24. THE DEBATES IN THE FEDERAL CONVENTION OF 1787 REPORTED BY JAMES MADISON 545 (Gaillard Hunt & James B. Scott eds., 1920).

25. U.S. CONST. art. I, § 8, cl. 8.

26. *See supra* note 10 and accompanying text.

27. *See* Bonito Boats v. Thunder Craft Boats, 489 U.S. 141, 150-51 (1989).

To be patentable and thus deserving of protection under the United States patent laws, an inventor is required to demonstrate that the subject matter of the invention falls within one of the four statutory patentable areas: (1) new and useful processes, (2) machines, (3) manufacture, and (4) compositions of matter.[28] If the subject matter of the invention is patentable the inventor must further demonstrate that it has a practical utility,[29] that the invention is novel,[30] and that the invention is non-obvious over the prior art.[31] Only when the invention satisfies each of these statutory requirements can a U.S. patent issue for that invention. Once a patent is granted, the inventor obtains several important legal rights, not the least of which is the right to exclude others from making, using, or selling the patented invention in the United States for the statutory monopoly period, currently twenty years from the date the patent application was filed.[32]

A. *Utility*

The patent statute 35 U.S.C. § 101[33] broadly defines patentable subject matter as "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."[34] To satisfy utility the invention must confer on society some tangible benefit.

Prior to the human genome publication gene-based inventions had little difficulty in satisfying the utility requirement because the threshold the courts used to satisfy utility was minimal.[35] The statutory requirement was simply that the claimed

28. These statutory bases are set forth in 35 U.S.C. § 101.

29. Utility is governed by 35 U.S.C. § 101. *See infra* Part III-A and accompanying notes.

30. Novelty is governed by 35 U.S.C. § 102 (2003). *See infra* Part III-B and accompanying notes.

31. Non-obviousness is governed by 35 U.S.C. § 103 (2003). *See infra* Part III-C and accompanying notes.

32. *See supra* note 9 and accompanying text.

33. 35 U.S.C. § 101.

34. *See id.*

35. *See, e.g., Ex parte* Drulard, 223 U.S.P.Q. (BNA) 364 (Bd. Pat. App. & Int. 1983) (holding patentable a portable lightning rod which, even though potentially unsafe, was sufficiently useful to satisfy 35 U.S.C. § 101's utility requirement).

invention must have some practical application or use.[36] The product did not have to be superior to any current product, it merely had to be "useful." The utility standard was expanded somewhat for chemical agents during the 1950's to the extent that no utility was found for chemicals that had only speculative use; a "specific" use became the requirement.[37] The utility requirement was considered by the U.S. Supreme Court in *Brenner v. Manson*.[38] Inventor Manson filed an application to patent a process for producing certain steroids and requested "interference" be declared to establish that his patent application had priority over a patent that had issued in the year previous to his application allegedly covering the same process.[39] Manson's patent application was rejected by the PTO for failure to "disclose any utility for" the compound produced by the process.[40] In appealing the decision, Manson noted that steroids of the class which included the compound produced by his process were undergoing screening for possible tumor-inhibiting effects in mice. A homologue[41] of his steroid had proven effective in that test.[42] Manson also argued that his process was "useful" in that it produced a product that belonged to a class of compounds

36. Courts have often seen fit to allow market forces to determine an invention's societal benefit when considering whether a new invention is of lesser or greater benefit to society than a preexisting invention of the same type. *See e.g.*, Lowell v. Lewis, 15 F. Cas. 1018, 1019 (D. Mass. 1817) (No. 8565) (holding that inventions that are not more useful than other similar inventions of that type "will silently sink into contempt and disregard").

37. *See, e.g., In re* Bremmer, 182 F.2d 216 (C.C.P.A. 1950). In this case the patent application disclosed a novel chemical structure but did not assert any specific use for that chemical. *Id.* The court found the patent invalid for failure to satisfy the 35 U.S.C. § 101 utility requirement, holding that disclosure of a new chemical compound required a disclosure of some specific asserted utility for that compound. *Id.* The court, however, did not specify what a specific utility is, thereby maintaining a low threshold for satisfying the statutory requirement.

38. Brenner v. Manson, 383 U.S. 519 (1966).

39. The right to a patent in the U.S. is based on a first to invent system. Thus, a party who is second to file a patent application may nevertheless be awarded the patent if he can prove that he was the first to invent. The procedure by which priority is determined is called an "interference." Interference actions are conducted within the PTO but are similar to judicial actions in most respects. *See generally* 1 CHISUM ON PATENTS (2003).

40. *Manson*, 383 U.S. at 521.

41. A homologue (or homolog) is a chemical compound having a structural similarity with another compound. *See* MOLECULAR BIOLOGY OF THE CELL, *supra* note 5, at G:17.

42. *Manson*, 383 U.S. at 522.

that were the subject of serious scientific research.[43] The Court disagreed with Manson's arguments and it held that a process that results in a product whose only established utility is an object of further scientific inquiry does not satisfy the statutory utility requirement.[44] The Court also rejected the argument that utility of a chemical compound can be established by showing that it is structurally homologous to related chemicals having established utility.[45] Thus, the Court suggested that, for chemical compounds,[46] prediction of function based on structural homology will not satisfy the utility requirement without some additional testing to demonstrate a product's usefulness.[47]

B. *Novelty*

The patent applicant also must demonstrate that his invention is novel. Novelty is governed by 35 U.S.C. § 102.[48] Occurrence of any of the following situations will preclude the invention's patentability: It was already (1) patented in the United States or a foreign country;[49] (2) described in a printed

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43. *Id.* at 532.

44. *Id.* at 535-36:

> We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product. That proposition seems to us little more that an attempt to evade the impact of the rules which concededly govern patentability of the product itself. . . . [A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

Id.

45. The Court stated: "Even on the assumption that the process would be patentable were respondent to show that the steroid produced had a tumor-inhibiting effect in mice, we would not overrule the Patent Office finding that respondent has not made such a showing." *Id.* at 531-32.

46. Genes have been treated like chemical compounds for many patentability purposes. *See infra* Part IV.

47. This is because, as the Court noted, the properties of some chemicals are unpredictable. *Manson,* 383 U.S. at 532. Later holdings have established that experimental testing of compounds to establish their utility as effective in humans does not require actual testing in humans; utility will be established if the testing is done in the laboratory using a system whose results are known to be predictive of results in the body. *See, e.g.,* Fujikawa v. Wattanasin, 93 F.3d 1559, 1564-65 (Fed. Cir. 1996).

48. *See* 35 U.S.C. § 102.

49. *See* 35 U.S.C. § 102(a).

publication in the United States or a foreign country;[50] or (3) known, used, or offered for sale by others in the United States.[51] The novelty requirement may prove to be a formidable bar to patentability of genes because the publication of the human genome would anticipate that claimed gene and create a prima facie case for lack of novelty, barring its patentability.[52]

C. *Non-Obviousness*

Whereas the 35 U.S.C. § 102 novelty requirement insures that the claimed invention is new, the non-obvious requirement insures that the claimed invention represents a significant improvement over the prior art.[53] According to 35 U.S.C. § 103,[54] a patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art 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."[55] Subsequent to the publication of the human genome, the non-obviousness requirement will impose additional hurdles in obtaining property on gene-based inventions.

Determination of the non-obviousness of a claimed invention requires a three part test:[56] (1) a case-by-case analysis of

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50. *See* 35 U.S.C. § 102(b): To be anticipated, all of the elements of a patent claim must be present in a single publication. The publication must occur more than one year prior to the filing date of the patent application.

51. *See* 35 U.S.C. § 102(a). The use or sale of the invention must have occurred more than one year prior to the filing date of the patent application.

52. In addition to the 35 U.S.C. § 102 requirements, the patent application disclosure must enable one of ordinary skill in the art to "make or use" the invention. The enablement requirements are governed by 35 U.S.C. § 112. *See infra* Part V.

53. *See* 35 U.S.C. § 103.

54. *See id.*

55. *See id.* § 103(a).

56. *See* Graham v. John Deere, 383 U.S. 1 (1966). The *Graham* court stated that although "the ultimate question of patent validity is one of law . . . the § 103 condition lends itself to several basic factual inquiries." *Id.* at 17. According to the Court these inquiries are: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; and (3) the level of ordinary skill in the pertinent art. *Id.* Against this background, the obviousness of the claimed subject matter is determined. In addition, the Court discussed the importance of what are known as secondary considerations to the question of obviousness: "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circum-

the scope and content of the prior art; (2) a determination of the differences between the prior art and the invention; and (3) a determination of the level of skill of the ordinary worker in that art at the time the invention was made. A critical consideration for biotechnology inventions is that the scope of knowledge and technical expertise in these arts is expanding exponentially making it increasingly difficult to justify the non-obviousness of these inventions.[57] An early case testing the limits of non-obviousness to the developing field of biotechnology was *In re O'Farrell*.[58] In this case, the PTO examiner issued a final rejection of the application based on 35 U.S.C. § 103[59] obviousness over a combination of prior art references disclosing techniques for producing recombinant proteins, that was upheld by the PTO Board.[60] The inventors argued that the invention could not have been obvious due to the significant unpredictability in the field of molecular biology at the time of the patent application.[61] The court rejected this argument holding that unpredictability *per se* was not controlling; what was critical in a 35 U.S.C. § 103[62] non-obviousness analysis was whether one of ordinary skill in that art would have considered that prior art techniques employed were *likely to succeed*.[63]

Given this rather loose standard, it would appear that as biotechnology grew in complexity and the predictability of its techniques became accepted, there could come a time when almost any "new" biotechnology invention would arguably fail to meet the non-obviousness requirement. Possibly recognizing

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stances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or non-obviousness, these inquiries may have relevancy." *Id.* at 17-18.

57. For the biochemistry and molecular biology arts the courts have held that the level of skill of the ordinary skilled worker is at the post-graduate level, i.e., an M.D. or Ph.D. degree or its equivalent. *See* Merck & Co. v. Teva Pharms. USA, Inc., No. 01-048-JJF, 2003 U.S. Dist. LEXIS 15235, at *66 (D. Del. Aug. 28, 2003).

58. *See In re* O'Farrell, 853 F.2d 894 (Fed. Cir. 1988).

59. 35 U.S.C. § 103.

60. *O'Farrell*, 853 F.2d at 895.

61. *Id.* at 902.

62. 35 U.S.C. § 103.

63. *Id.* at 903. As the court stated: "Obviousness does not require absolute predictability of success. Indeed, for many inventions that seem quite obvious, there is no absolute predictability of success until the invention is reduced to practice . . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *Id.* (citations omitted).

this dilemma, later courts, construing the non-obviousness requirement for biotechnology inventions, increased the degree of certainty required to satisfy a finding of "reasonable expectation of success." For example, in *In re Deuel*,[64] a case involving recombinant produced cell growth factors,[65] the examiner (and later the PTO Board) rejected claims to the gene for these growth factors and the methods of producing the gene-products (proteins) recombinantly under 35 U.S.C. § 103 obviousness[66] because the protein sequence[67] had already been disclosed and methods of producing recombinant proteins were well established.[68] The Federal Circuit reversed, holding that the disclosure of a protein sequence does not render the gene sequence for that protein obvious,[69] the most that it does is to make it "'[o]bvious to try' [which] has long been held not to constitute obviousness."[70] By this holding, the *Deuel* court narrowed the "reasonable expectation of success" standard[71] of the 35 U.S.C. § 103[72] obviousness test (at least as it applies to recombinant proteins) to exclude inventive steps that, while arguably being

64. *In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995).

65. The growth factors were a class of proteins called heparin-binding growth factors involved in stimulating cell division (mitogenesis) and DNA repair. *See* L.W. Haynes, *Fibroblast (Heparin-Binding) Growth Factors in Neuronal Development and Repair*, 2 MOL. NEUROBIOL. 263 (1988).

66. 35 U.S.C. § 103.

67. Proteins are biological molecules of enormous importance and comprise a class that includes, *inter alia*, enzymes, growth factors, receptors, neurotransmitters, structural materials and hormones. Proteins consist of polymers of amino acids connected by peptide bonds; each amino acid is encoded for by the corresponding triplet codon in the gene for that protein. If the protein represents less than the entire gene it is referred to as a peptide. The individual amino acids of the protein can either be deduced from its corresponding genetic code or can be measured directly by a technique called protein sequencing. *See generally* MOLECULAR BIOLOGY OF THE CELL, *supra* note 5, at 129-58.

68. *See Ex parte* Deuel, 33 U.S.P.Q.2d 1445 (Bd. Pat. App. & Int. 1993).

69. The court reasoned that the present invention was the DNA encoding the protein, not the protein itself (which was taught in the prior art). *See In re* Deuel, 51 F.3d 1552, 1558 (1995). Because of the redundancy of the genetic code, that is, for many amino acids there are several different DNA sequences that can encode them, describing a protein sequence does not expressly describe the DNA sequence. *Id.*

70. *Id.* at 1559.

71. *See In re* O'Farrell, 853 F.2d 894, 904 (1988).

72. 35 U.S.C. § 103.

"likely" to succeed, nevertheless include the "possibility" of failure.[73]

This ruling, however, created a dilemma; on the one hand it was arguably necessary to prevent recombinant protein inventions from becoming unpatentable due to obviousness. On the other hand the ruling created a fiction by ignoring that by 1993 (the year of the *Deuel* decision[74]), the technical capabilities of the ordinary molecular biologist had increased to the point where it was "cookbook" to create a recombinant protein once the protein sequence was known.[75] Thus, the court's perceived fear of limiting the scope of patentable biotechnology inventions may have forced them to create a standard out-of-touch with the technical realities of the field and, in so doing, create confusion regarding patentability standards of these inventions.

IV. Patentability of DNA

The first case specifically outlining the patentability requirements for DNA was *Amgen v. Chugai Pharmaceutical*.[76] In this case, Amgen had been awarded a patent whose claims included, *inter alia*, the cDNA[77] for the gene encoding human erythropoietin (EPO).[78] Amgen's EPO cDNA claims were broad and as written included the entire universe of EPO cDNAs, including those from other animal species. The only practical limitation in the claims was that the EPO must be capable of stimulating red blood cell production, that is, the gene was now

73. In the *O'Farrell* court's analysis the possibility of failure is described as "the possibility of unexpected results." *O'Farrell*, 858 F.2d at 903.

74. *Ex parte* Deuel, 33 U.S.P.Q.2d 1445 (Bd. Pat. App. & Int. 1993).

75. *See* JOSEPH SAMBROOK ET AL., MOLECULAR CLONING: A LABORATORY MANUAL (2d ed. 1989).

76. 927 F.2d 1200 (Fed. Cir. 1991).

77. cDNA, or coding DNA, is the portion of the gene that contains the information that is used to produce the protein the gene encodes. The cDNA is converted into protein by a series of steps that includes first, the transfer of the genetic information from the cDNA to a corresponding mRNA (messenger RNA) within the cell's nucleus. The mRNA is then transported into the cell's extra-nuclear compartment where it is converted into the corresponding protein by a process called translation. *See generally* 7 GENES, *supra* note 4, at 119-37.

78. EPO is a hormone-like protein produced in the kidney that stimulates the production of red blood cells in the bone marrow. EPO levels are reduced in patients with kidney disease which results in some cases in life-threatening anemia requiring chronic blood transfusions. Kidney patients receiving pharmaceutical EPO often become transfusion independent.

defined not by its structure but by its function.[79] The *Amgen* court held that a generic DNA claim could only be patentable[80] by disclosure in the patent specification of a sufficient number of DNA species to demonstrate that the inventors knew how to make and use the genus of EPO DNA's they were claiming.[81] Since the court found that Amgen only disclosed a few EPO DNA species, they were not entitled to claim the entire genus, and invalidated the broad EPO DNA claims.[82] What is most significant in the *Amgen* decision is that the court refused to allow a gene to be described by its function; they required that it be described by its structure, that is, the precise recitation of the nucleic acids that constitute the DNA for that gene.[83]

Two years later the court revisited the requirements for DNA patentability in *Fiers v. Revel*.[84] The *Fiers* case began as a patent interference action[85] in the PTO[86] between three foreign inventors who each claimed, *inter alia*, to have been the first to invent the cDNA encoding the human protein beta-interferon (B-IF).[87] The PTO did not award the invention to Fiers, but to another inventor, Sugano, and Fiers appealed the PTO's decision.[88] The Federal Circuit affirmed the PTO's decision holding that Fiers did not conceive of the invention[89] because his origi-

79. Essentially any EPO whether from humans or closely related mammals is capable of performing this function.

80. The *Amgen* court's patentability argument was based on the 35 U.S.C. § 112 enablement requirement. *See Amgen*, 927 F.2d at 1213-14; 35 U.S.C. § 112.

81. *See Amgen*, 927 F.2d at 1213-14.

82. *Id.*

83. *See id.* at 1214.

84. 984 F.2d 1164 (Fed. Cir. 1993).

85. *See* CHISUM, *supra* note 39.

86. *Fiers*, 984 F.2d at 1166.

87. Interferon is a protein that promotes cellular resistance to viral infection. *See* T.C. Merigan, *Interferons of Mice and Men*, 276 N. ENG. J. MED. 913 (1967).

88. *See Fiers*, 984 F.2d at 1164.

89. Conception is the touchstone of "invention." It is the mental part of inventiveness. In the United States, the first inventor to conceive the invention is the one who is awarded patent protection, so long as the inventor reduces the invention to practice (i.e., provides information or an actual prototype that shows how to use the invention for its intended purpose) and does not abandon, suppress, or conceal the invention. *See* 35 U.S.C. § 102(g) (A person shall be entitled to a patent unless . . . (g) before the applicant's invention thereof the invention was made in this country by another who had not abandoned, suppressed, or concealed it).

nal application, from which he was claiming priority,[90] "disclosed a *method* for isolating a fragment of the DNA coding for B-IF, but did not disclose a complete DNA *sequence* coding for B-IF."[91] The court re-affirmed the principles set out in *Amgen* that a gene cannot be described by its biologic function but only by its structure: "The present [invention] is to a product, a DNA which codes for B-IF; it is a claim to a product having a particular biologic activity or function, and in *Amgen*, we held that such a product is not conceived until one can define it other than by its biologic activity or function."[92] The court went on to explain: "An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."[93] Because Sugano, but not Fiers, disclosed the entire nucleotide sequence of the B-IF cDNA in his patent application, Sugano was awarded priority of the invention.[94]

The most recent case in the gene patentability "trilogy" is *Regents of University of California v. Eli Lilly*,[95] decided four years after *Fiers*. This case was a patent infringement action relating to recombinantly produced insulin.[96] The University's patent contained claims for recombinantly produced *human* in-

90. Priority in the patent regime is the date at which the patent application was filed, but the patent will only be valid if the application's claims, as filed, met all of the statutory requirements for patentability.

91. *Fiers*, 984 F.2d at 1167 (emphasis added).

92. *Id.* at 1169.

93. *Id.* at 1170. But the standards for satisfying the written description requirement for genes may be evolving as demonstrated by the recent Federal Circuit decision that reversed its prior position. It held that written description of a gene can be satisfied by reference in the patent application of a deposition made into a public depository of a cell or other genetic material containing the claimed gene, even if the inventors did not disclose the gene sequence in the application. *See* Enzo Biochem, Inc. v. Gen-Probe, Inc., 296 F.3d 1316 (Fed. Cir. 2002).

94. *See Fiers*, 984 F.2d at 1164.

95. 119 F.3d 1559 (Fed. Cir. 1997).

96. Insulin is a protein hormone produced in the pancreas and secreted into the bloodstream and is required for the cellular metabolism of glucose. Insulin deficiency may result in diabetes, which, in severe cases, requires daily injections of insulin. Until the advent of recombinant protein biotechnology, insulin was produced from pancreatic tissue of animals, which could, in some cases, cause allergic reactions in sensitive individuals. Recombinant protein biotechnology allowed for the production of *human* insulin which is much less likely to cause allergic reactions. *See id.* at 1562.

sulin although the patent specification disclosed the DNA sequence of *rat* insulin only. The University argued that by disclosing the nucleotide sequence for *rat* insulin, combined with the knowledge in the molecular biology arts of the methods for obtaining cDNAs, they had enabled one of ordinary skill to make *human* insulin cDNA.[97] The court disagreed, upholding the *Amgen/Fiers* requirement that DNA be described (for purposes of 35 U.S.C. § 112 enablement) by its nucleotide sequence, not by its function.[98] Thus, by these three cases, the Federal Circuit seemingly established a bright-line rule that for purposes of gene patentability, a gene is defined by its structure (i.e., its DNA sequence) and not by its function (i.e., its biologic activity).

V. Patentability of Genes Following the Human Genome Publication

Since the Federal Circuit has defined a gene by its *DNA sequence* for purposes of patentability, there is little doubt that the publication of the complete human genome results in the unpatentability of all human genes described in that publication by virtue of failing the test of 35 U.S.C. § 102(b).[99] As a result, claims to naturally occurring human genes or gene fragments in applications submitted after February 16, 2002[100] are

97. *See Lilly*, 119 F.3d at 1567.

98. *Id.* As the *Lilly* court stated:

> The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of [human insulin].

Id.

99. *See supra* Part III-B.

100. The Celera/HGP collaboration published their results on February 16, 2001. *See* Venter et al., *supra* note 5, at C1. Therefore, for a 35 U.S.C. § 102(b) anticipation bar, patent applications containing claims to human genes or gene fragments filed after February 16, 2002 are anticipated and hence unpatentable by this publication. *See* 35 U.S.C. § 102(b).

unpatentable for lack of novelty.[101] Therefore, inventions subsequent to February 16, 2002 will no longer be able to monopolize claims to the genes themselves, but must rely instead on the patentability of some downstream product of the gene or gene fragment. This does not mean, however, that all human genes become unpatentable; only those genes described in the human genome publication are anticipated; gene variants, mutants, or polymorphisms not described in the human genome publication remain patentable in so far as they are not anticipated. Moreover, not all of the approximately 30,000 "predicted" human genes have been structurally defined as of this writing, and those "predicted" but as of yet undefined genes remain patentable until 1 year after they are structurally defined by DNA sequencing.

A. *Obviousness of Gene-Based Inventions*

In addition to the anticipation and hence unpatentability of the genes themselves resulting from the genome publication, there are issues concerning whether other types of gene-based inventions are made obvious and hence unpatentable. As discussed in Part III-C, the standards for 35 U.S.C. § 103 non-obviousness are derived from the *Graham* case,[102] and include: (1) a case-by-case analysis of the scope and content of the prior art; (2) an examination of the differences between the prior art and the claims at issue; and (3) an ascertainment of the level of ordinary skill of a person working in the pertinent art.[103] To restate the test in another way; an invention would be obvious if a combination of the universe of knowledge in that discipline (i.e., the scope and content of the prior art) and the technical expertise of a person working in that discipline (i.e., the ordinary skilled person) would have motivated that person to create the invention.[104] Thus, it is apparent that non-obviousness becomes more

101. *See supra* Part III-B.

102. *See* Graham v. John Deere, 383 U.S. 1 (1966).

103. In addition, the Court can also use objective indicia of non-obviousness, such as commercial success, long-felt but unresolved needs, and failure of others in performing the non-obvious analysis. *Id.* at 17-18.

104. The motivation is what distinguishes non-obviousness from "obvious to try," a condition the courts have held does not constitute obviousness. *See In re* O'Farrell, 858 F.2d 894 (Fed. Cir. 1988); *In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995); *supra* Part III-C.

difficult to establish as the universe of knowledge in that art and the technical expertise of its practitioners increases (i.e., *Graham* elements 1 and 3[105]).

In applying this rationale to gene-based inventions, it may prove more difficult to defend against an obviousness challenge for the following reasons. First, the universe of knowledge in the biotechnology arts encompasses many disciplines which are highly developed technically (e.g., molecular biology, biochemistry, protein chemistry, computer sciences, cell biology, genetics, genomics, medicinal chemistry, pharmacology, etc.). Secondly, the skill level of the ordinary biotechnology practitioner is highly advanced.[106] Thus, it will be increasingly difficult to demonstrate that gene-based inventions are not made obvious by the increasingly expansive scope of the biotechnology prior art combined with the high level of skill of its practitioners.[107] At the very least, recognizable demarcations between obvious and non-obviousness gene-based inventions are likely to become blurred.

B. *Gene-Based Inventions and the Utility Requirements*

Even if gene-based inventions can avoid 35 U.S.C. § 103 obviousness concerns, they still must satisfy the patentability requirement of having a "specific," "substantial," and "practical" utility.[108] For chemical or recombinant protein inventions, courts have maintained that utility can be satisfied by demonstrating that the compound has an experimentally validated biologic effect or is an intermediate in a known biochemical

105. *See* 383 U.S. at 17.

106. For example, the level of ordinary skill of molecular biologists, pharmacologists, chemists, and computer scientists are considered to be Ph.D's. *See* Ajinomoto v. Archer-Daniels-Midland, C.A. No. 95-218-SLR, 1998 U.S. Dist. LEXIS 3833, *126 (D. Del. March 13, 1998). But education level is but one factor articulated by the courts' that is relevant to a determination of the level of ordinary skill. The others are: type of problems encountered in the art, prior art solutions, rapidity of innovation, and sophistication of the technology. *See also* Bausch & Lomb v. Barnes-Hind/Hydrocurve, 796 F.2d 443, 449-50 (Fed. Cir. 1986).

107. The obviousness challenge could be asserted by the examiner during prosecution of the application or by the alleged infringer subsequent to patent issuance.

108. *See supra* Part III-B.

pathway.[109] But the corollary to this is that compounds having only a hypothetical, or experimentally unvalidated biological effect, or whose usefulness is simply as a research tool, will not satisfy the 35 U.S.C. § 101 practical utility requirement.[110]

Within this framework, it is likely that gene-based inventions *subsequent* to human genome publication will have an uphill battle in establishing practical utility unless the actual biological function of the gene is experimentally validated, either through the inventor's own research or by the prior art.[111] In that case, a showing of substantial structural homology[112] be-

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109. *See In re Bremmer*, 182 F.2d 216, 216 (C.C.P.A. 1950). *See, e.g.*, Genentech v. Chiron Corp., 220 F.3d 1345, 1354 (Fed. Cir. 2000). This case stems from an interference action in the PTO between Genentech and Chiron over a patent dispute concerning the recombinant protein human insulin-like growth factor-I. When Genentech filed their patent application they did not know the *in vivo* biologic target for this protein, the only data they had was that it was bound to a cellular receptor for the protein in the laboratory. The district court found that this was enough to satisfy the practical utility requirement and awarded priority of the invention to Genentech. *Id.* The Federal Circuit reversed holding that without data showing the actual biologic "activity" of the protein, the inventors had not determined "the intended purpose of the invention." *Id.*; *accord Ex parte* Maizel, 27 U.S.P.Q.2d (BNA) 1662, 1668 (Bd. Pat. App. & Int. 1992). In *Maizel*, the PTO Board, in affirming the examiner's final rejection of Maizel's application, indicated that a claimed recombinant protein (B-cell growth factor) whose biological function was unknown as of the time of the patent application, would probably fail the statutory utility requirement. (The examiner ultimately rejected the application for reasons unrelated to utility). This was true despite the fact that the protein shared structural similarity with proteins speculated to act as immune response modulators. *Id. See also In re* Deuel, 27 U.S.P.Q.2d (BNA) 1360, 1365, (Bd. Pat. App. & Int. 1993), (where the PTO Board affirmed the examiner's final rejection of Deuel's application for a purified protein having only a speculative biologic function based on structural homology to other proteins).

110. *See, e.g.*, Brenner v. Manson, 383 U.S. 519, 535 (1966) (where a compound's usefulness as a research tool did not satisfy the utility requirement).

111. A relatively recent technique used to predict a gene's biologic function is by use of combinations of molecular biological and computer analysis called proteomics. The drive to define the biologic functions of newly discovered genes has spawned a cottage industry of academic consortiums and proteomics companies that hope to utilize this information for pharmaceutical applications. However, it is unclear whether the PTO or the courts will accept a predicted biologic function based on proteomics as an actual demonstration of utility. *See, e.g.*, SWISSPROT, THE HUMAN PROTEOMICS INITIATIVE, *at* http://us.expasy.org/sprot/hpi/hpi_desc.html (last visited Dec. 3, 2003).

112. Structural homology is most often established using computer algorithms, for example, the BLAST® (Basic Local Alignment Search Tool) program, which compares a DNA or protein sequence to sequence databases and reports a statistical score for the comparisons. National Center for Biotechnology Information Homepage *at* http://www.ncbi.nlm.nih.gov/BLAST (last visited Dec. 3, 2003).

tween the newly discovered gene and other genes whose biologic functions are experimentally validated will most likely satisfy the statutory utility requirement. By contrast, newly discovered genes sharing no substantial structural homology to genes with known biologic function will likely fail the statutory utility requirement and be unpatentable.[113] Hence, it is doubtful that the identification of "new" genes stemming from the human genome publication will, in and of itself, satisfy utility patentability standards (and therefore will be commercially impractical) until the actual biologic function(s) of those genes are known.[114]

Undoubtedly, one likely commercial application for newly discovered genes will be the development, however, of pharmaceuticals targeting the gene product(s). Pharmaceutical development is a labor-intensive and costly undertaking typically unsuited for academic research programs or small-cap biotech companies.[115] Thus, one likely result of the human genome publication will be the stimulation of collaborative ar-

113. *See, e.g.*, Revised Interim Utility Guidelines Training Materials (Jan. 5, 2001), *available at* http://www.uspto.gov/web/menu/utility.pdf. Example 9 is directed to genes whose protein products have no known biologic function, in which case the examiner is instructed to reject the claim for lack of utility. *Id.* at 50-53. Example 10 is directed to a gene whose protein product has 95% structural homology to other proteins with known biologic activity, in which case the examiner is instructed not to reject for lack of utility. *Id.* at 53-55. It is noteworthy that the gene in Example 9 is found to be without patentable utility despite the fact that the gene can be used as a molecular probe.

114. The departure of Dr. Craig Venter, the founder of Celera Genomics, from the company leadership is evidence of the lack of commercial utility of newly discovered genes *per se*. Celera, apparently recognizing that the commercial utility of the genome is in pharmaceutical development, not in the genes themselves, decided to replace Dr. Venter with a CEO with pharmaceutical experience. Pollack, *supra* note 21.

115. The average cost to bring a new drug to market is estimated to be $500 million. It is further estimated that it takes an average of 12-15 years to discover and develop a new medicine. A significant portion of the cost of drug development stems from the strict requirements for efficacy, safety, and clinical studies mandated by the Food and Drug Administration (FDA) for drugs sold in the United States. *See* THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, WHY DO PRESCRIPTION DRUGS COST SO MUCH . . . AND OTHER QUESTIONS ABOUT YOUR MEDICINES 2, *available at* http://www.phrma.org/publications/publications/brochure/questions/questions.pdf (last visited Dec. 22, 2003). This is one reason why many American-manufactured pharmaceuticals are evaluated clinically and first released into European markets where regulatory scrutiny is considerably less stringent. *See* Jennifer Kulynych, *Will FDA Relinquish the "Gold Standard" for New Drug Approval? Redefining "Substantial Evidence" in the FDA Moderniza-*

rangements between large-cap pharmaceutical companies and academic research institutions and small-cap biotechnology companies, where licensing arrangements could provide for shared risks and rewards for gene-based pharmaceutical development.[116]

C. *Gene-Based Inventions and the Enablement Requirements*

In addition to the requirements that an invention must be novel,[117] non-obvious,[118] and have a practical utility,[119] to be patentable the invention must also satisfy the 35 U.S.C. § 112 enablement requirement.[120] This requirement refers to the obligation that the inventor must describe how to make and use the invention to one of ordinary skill in the pertinent art.[121] The purpose of this requirement is to ensure that the public can benefit from the invention.[122] The standard for determining whether the patent disclosure complies with the enablement requirement does not preclude that some experimentation by the ordinary skilled worker is necessary to practice the invention; but the amount of experimentation "must not be unduly extensive."[123] The courts have interpreted the statute to require that the claimed invention be enabled by the disclosure so that one

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tion Act of 1997, 54 FOOD DRUG L.J. 127, 138-39 (1999). *See generally* Michael Barum et al., *Patent Rights And Licensing*, 6 B.U. J. SCI. & TECH. L. 3 (2000).

116. *See* Barum et al., *supra* note 115, ¶¶ 47-49.

117. Governed by 35 U.S.C. § 102; *see supra* Part III-B.

118. Governed by 35 U.S.C. § 103; *see supra* Part III-C.

119. Governed by 35 U.S.C. § 101; *see supra* Part V-B.

120. 35 U.S.C. § 112. The enablement requirement actually includes two distinct requirements that are both found in the first paragraph of the statute. The first requirement refers to the aforementioned obligation to allow one of ordinary skill to "make and use the invention." *Id.* The second requirement is that the inventor "is in possession of the invention" as of the date of filing the application. *Id.* This latter requirement is referred to as the "written description" requirement and was discussed *supra* in Part IV regarding the patentability of DNA sequences.

121. Atlas Powder v. Dupont, 750 F.2d 1569, 1576 (Fed. Cir. 1984) ("To be enabling under § 112, a patent must contain a description that enables one skilled in the art to make and use the claimed invention.") (citation omitted).

122. *See* CHISUM ON PATENTS § 7.03 (2003) ("The policy behind Section 112 is to make a patented invention fully available to the public without any requirement of such arduous research.").

123. *Atlas Powder*, 750 F.2d at 1576.

of ordinary skill can make and use it without "undue experimentation."[124]

1. *Undue Experimentation: The Wands Factors*

In *In re Wands*, the court identified eight factors to consider in determining whether one having ordinary skill in the art would be required to perform "undue experimentation" to practice a claimed invention. These factors are: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (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.[125]

It is clear that the *Wands* factors are dynamic; that is, they will vary with the development of the knowledge base of a given discipline and the skill of its practitioners. With that in mind, the *Wands* factors should provide the courts with a simple procedure for allowing the patentability standards of biotechnology of inventions to evolve as biotechnology evolves. Yet, this has not happened; the courts continue to apply a strict enabling requirement to biotechnology inventions, particularly to DNA claims.[126]

VI. Increased Litigation Due to Invalid Patents

There is little doubt that one result of the publication of the human genome will be a flood of new patent applications claiming the products and uses of the recombinant proteins of the newly discovered genes. Because the biologic activity of many of these genes and their protein products will be merely specu-

124. *See In re* Wands, 858 F.2d 731, 736-37 (Fed. Cir. 1988) ("Enablement is not precluded by the necessity for some experimentation . . . . However, experimentation needed to practice the invention must not be undue experimentation.").

125. *Id.* at 737.

126. *See, e.g.*, Enzo Biochem. v. Calgene, 188 F.3d 1362 (Fed. Cir. 1999), where the court, applying the *Amgen/Fiers/Lilly* rationale (*See supra* Part IV), held that the patent's broad claims to the use of antisense DNA technology (a technology that inhibits protein synthesis by preventing the expression of the gene encoding that protein) were not enabled because the specification disclosed only a limited number of examples for bacterial genes and such limited disclosures were not commensurate with the broad scope of the patent claims.

lative at the time of patent application, this is likely to produce an increase in the number of patentability disputes in the PTO as well as increased litigation concerning the validity of issued patents to these genes. This is particularly true for genes whose biologic activities are merely "predicted" based on structural homology.[127] Both the PTO[128] and the courts have recognized that a "predicted" function based on structural homology to compounds having a known practical use satisfies the practical utility requirement,[129] but neither have defined the amount of structural homology that will suffice for this purpose, particularly as this relates to protein homology. The examples provided in the most recent PTO Utility Guidelines suggests that the extent of structural homology between proteins required to satisfy practical utility must be extremely high.[130] The problem here is that it has long been known in the protein biochemistry art that there is not a direct relationship between the extent of

127. *See supra* note 111 and accompanying text.

128. The PTO rejected the arguments that the use of computer-based analysis to assign functions to newly discovered genes based on homology to prior art proteins should not be allowed due to the unpredictability of the assignments. It held that "when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." Utility Interim Guidelines, 66 Fed. Reg. 1092, 1096 (Jan. 5, 2001).

129. A biotechnology case discussing the use of structural similarity to evidence practical utility is Kridl v. McCormick, 105 F.3d 1446, 1451 (Fed. Cir. 1997), in which the invention consisted of the use of anti-sense recombinant DNA technology to make virus-resistant plants. The court held that "[t]he utility of the invention need not always be explicitly corroborated. Circumstances may make a utility implicit, as they did here. The evidence here indicates that a person of ordinary skill in the art would have accepted [the inventor's] testimony of intended use of his invention at the time of his conception." Thus, the court, while not ruling directly on the structural homology issue, found that for some biotechnology inventions, such as anti-sense recombinant proteins, the utility of the invention is inherent in the invention itself. While this holding may provide guidance for anti-sense recombinant protein inventions it does little to offer guidance for traditional (i.e., "sense") recombinant protein inventions. *See also* Rey-Bellet v. Schindler, 493 F.2d 1380 (C.C.P.A. 1974); *In re* Brana, 51 F.3d 1560, 1567 (Fed. Cir. 1995), ("[E]vidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility."). *But see In re* Joly, 376 F.2d 906, 908 (C.C.P.A. 1967) (compounds whose only known utility was to provide for further research did not satisfy the utility requirements for patentability).

130. *See supra* note 113 and accompanying text.

structural homology between proteins and their biologic properties.[131] Therefore, the PTO may have created patentability standards that are in conflict with the realities concerning protein structure/function relationships.[132] This conflict will likely precipitate litigation as the courts attempt to resolve this issue.

VII. Economic Considerations: Increased Licensing Due to Uncertainty of Patentability

Until the courts resolve the many complex issues concerning the validity of patents claiming genes and their encoded proteins in light of the publication of the human genome, there will remain considerable uncertainty as to the commercial value of property rights to many of these inventions. Considering that the costs of litigation for biotechnology patents is extremely high, estimated to exceed one million dollars for the average litigation,[133] combined with the fact that biotechnology patents are more frequently litigated than any other kind of technology,[134] it may be advantageous for patentees to distribute the risks involved in potential litigation by licensing inventions rather than maintaining exclusive rights to them.[135]

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131. For example, proteins with as little as 40% structural homology may share nearly identical biologic properties. *See, e.g.*, Y. Naoi et al., *The Functional Similarity and Structural Diversity of Human and Cartilaginous Fish Hemoglobins*, 307 J. MOL. BIOL. 259-70 (2001).

132. The flip side is that if there is substantial structural homology between a prior art protein whose biologic activity is known and the newly discovered protein (gene) then this could arguably result in the finding that the newly discovered protein was obvious compared to the prior art and hence unpatentable. Such a result occurred in *In re* Mayne, 104 F.3d 1339, 1342 (Fed. Cir. 1997). In this case, the inventors challenged a final rejection of their patent application pertaining to the production and use of recombinant proteins. The PTO Board rejected the application on the basis of § 103 obviousness of the present invention based on the structural similarity of the recombinant proteins to those in the prior art. The Federal Circuit affirmed the rejection stating that "[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness.") (citation omitted).

133. *See* Mary Ann Tucker, *Corporate Counsel's Role In Patent Litigation*, *in* PRACTICING LAW INSTITUTE: PATENTS, COPYRIGHTS, TRADEMARKS, AND LITERARY PROPERTY COURSE HANDBOOK SERIES 279, 296 (1995).

134. *See* Barum et al., *supra* note 115.

135. A working theory is that if there are many "invalid" patents in an area of potential investment, this would: (1) discourage investment by increasing costs of entry, i.e., potential investors will have more patents to investigate for potential

Arrangements could be made that include contingencies in the event the patent application fails to issue or is subsequently invalidated.[136] Such arrangements could encourage development of products whose patentability is uncertain. This approach may be particularly significant to small-cap biotechnology companies whose product development decision-making is more likely influenced by patent litigation costs,[137] but will also be useful to academic research programs who are likely to benefit from risk-sharing arrangements.

VIII. Conclusions

The publication of the first draft of the human genome on February 16, 2001 will have the effect of making subsequent inventions claiming human genes or gene-fragments that were disclosed unpatentable due to lack of novelty (35 U.S.C. § 102) and obviousness (35 U.S.C. § 103).[138] The patentability of inventions claiming recombinant human proteins and products

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infringement or to license from; and (2) it will reduce the number of potential entrants because some patentees will not wish to dilute their property rights by licensing and others will not want to bear the high costs of litigation and/or licensing. From this reasoning an empirical formula can be developed whereby a rational investor will license when the costs of the license is less than the likelihood of success in the litigation multiplied by the likely infringement damages plus litigation costs.

136. In this regard, Aronson v. Quick Point Pencil Co., 440 U.S. 257 (1979), is illustrative. In this case, the patent applicants negotiated a contract with a manufacturing company for the manufacture and sale of a keyholder prior to their patent issuing. *Id.* at 259. The contract called for royalties to be paid to the patentee in return for an exclusive license to make and sell the keyholders. The amount of royalties were conditioned on the patent issuing within five years, if the patent failed to issue within that time the licensor's royalties would be reduced. *Id.* at 260. When the patent application was rejected by the PTO the licensor sued to hold the licensing arrangement void. The United States Supreme Court held that the license arrangements were enforceable contracts that were independent of product patentability. *Id.* at 262. This holding, therefore, protects the interests of both licensors and licensees by permitting shared risk in developing products whose patentability is uncertain.

137. *See* Josh Lerner, *Patenting In the Shadow Of Competitors*, 38 J.L. & ECON. 463, 465 (1995).

138. The 35 U.S.C. § 102(b) novelty bar begins for gene-based inventions after February 16, 2002; the 35 U.S.C. § 103 non-obviousness standard is measured from February 16, 2001. Also, as stated in *supra* Part V, gene variants, mutants, and polymorphisms not described in the human genome publication, as well as DNA sequences not yet recognized as genes remain patentable until one year after they are described in a printed publication.

associated with recombinant proteins will to a large extent depend upon whether they will be considered anticipated and obvious in light of the genome publication and the scope of prior biotechnology commercialization for that product. Application of previously commercialized products to newly discovered genes will have an uphill battle to defend against statutory anticipation and obviousness. Current standards for the 35 U.S.C. § 112 written description requirement[139] for genes will be mooted by the genome publication. Confusion as to what patentability standards apply following the genome publication will likely lead to increased litigation that could effect patenting decisions in both academic and commercial settings. Licensing of gene-based inventions may increase as a method for balancing risks until the courts consider what changes, if any, they are willing to make to accommodate the patentability issues raised by the genome publication. Ultimately, however, the publication of the human genome could stimulate much-needed reform regarding patentability standards for biotechnology inventions and hopefully result in increased predictability and efficiency for the commercialization of this rapidly evolving technology.

139. *See supra* Parts IV and V.