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THE HUMAN GENOME PROJECTS: PATENTING HUMAN GENES AND BIOTECHNOLOGY.

IS THE HUMAN GENOME PATENTABLE?

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I. INTRODUCTION: MOLECULAR BIOLOGY AND BIOTECHNOLOGY

This Article discusses legal issues involving invention, patent protection and commercialization of the products derived from studies of the human genome. Although the filed is not new, the recent emphasis on concerted efforts to develop therapeutics from information contained in the human genome has raised some interesting and difficult issues. [n.1] This Article is limited in scope to the following topics: issues of patent protection of DNA sequence information, proteins synthesized relying on DNA sequence information, processes used for making these proteins and uses to which the products of these processes are employed in treating human disease.

*462 The new issues raised by the Human Genome Projects [n.2] are most easily understood in the context of "traditional" biotechnology. The usual approach is based on determining the identification and function of the biochemicals involved, and then working "backwards" to identify the gene(s) responsible for the biochemicals' production. This section describes, in general terms, biotechnology as it has been in practice for the last 15 years. More recently, however, a new "structural" approach is being taken by many scientists working on the Genome Projects. This approach is very different from the "functional" approach, and brings different legal issues to the forefront of patent law. [n.3]

A. Purpose of Biotechnology

Simply defined, biotechnology is the use of biological processes to make products. Early examples include using yeast in the process of fermentation to produce bread, beer and wine. Later, selective cross-breeding produced desired characteristics such as greater meat production in cattle and higher yields in grains. As Gregor Mendel and other early scientists grew to understand the basis for inheritance, it became clear that some individualized traits (e.g., wrinkled seeds in pea plants) were passed to subsequent generations as if they were in discrete packets, with some offspring showing the trait and others not showing the trait. This discovery led to the development of the filed of

genetics. Mixing traits from different individuals (genetic recombination) of the same species is the basis of sexual reproduction, but such mixing requires reproductive compatibility. Cross-breeding through sexual reproduction is strictly limited by the ability to create viable offspring. Thus, a horse may cross-breed with a donkey and create a mule, but a horse cannot cross-breed with a tree.

B. The Development Of Modern Biotechnology

Two breakthrough discoveries lead to the development of the field of modern biotechnology. The first occurred in the early 1970s with the discovery of certain enzymes known as "restriction endonucleases," which can cut DNA in very specific places. Thus, for the first time, selective excision of a functional unit from DNA became possible. The second major discovery was of certain other enzymes, "DNA ligases," which can join pieces of DNA together to make a single, longer piece. As a result, the *463 creation of novel sequences of DNA became possible. [n.4] This ability to cause genetic recombination using molecular means, as opposed to sexual means, is the basis of modern biotechnology. Further, the patents on these processes and products became central to the new industry. [n.5]

These discoveries allowed scientists to insert foreign genes into cells, permitting them to make proteins which the cell had never been able to make before. Thus, a glow-in-the-dark tobacco plant could be made by inserting into the plant a gene which confers the ability to emit light, a property of the light organs of the common firefly. Similarly, new food products such as tomatoes which "ripen" before becoming soft (Flavr-SavrTM tomato) can be created, and, although picked "green," taste better than the usually available supermarket tomatoes. The field is rapidly expanding, and currently represents a multi-billion dollar industry. As the demand for new products expands, the business opportunities will increase.

The subset of biotechnology discussed here is aimed at human therapeutics. There are two main aims of therapeutic biotechnology: the treatment of symptoms of disease and the repair of fundamental genetic errors. The first aim is directed towards specific proteins which have certain therapeutic uses. An example is the use of human growth hormone to treat patients with congenital pituitary insufficiency resulting in retarded growth. By replacing the absent hormone with one made using biotechnology, patients grow and mature normally. A disadvantage with this strategy is the requirement for continued, long-term therapy. Also, recurrent treatment is needed because proteins are digested and removed by the body.

To overcome the problems in patients suffering from genetic diseases, scientists propose inserting the correct gene to replace the one that is defective. An example is the possible replacement of the defective Cystic Fibrosis Transmembrane Regulator (CFTR) gene in patients with a normal "gene." After the replacement of the defective gene with the normal gene, the affected cells would produce the needed protein themselves, thereby allowing the cell (and the person) to function normally. Because the cDNA is inserted

into the cells, it may last much longer than a protein injected into the body and may allow the cell to produce the needed protein for much longer periods of time. Therefore, this strategy promises to eliminate the need for recurrent therapy.

*464 C. Structure Of Genes And Protein Biosynthesis

Cells make proteins by relying upon the genetic information stored in cellular deoxyribonucleic acid (DNA). [n.6] DNA is a double helical chain of molecules, made of the nucleotide bases adenine (A), thymine (T), cytosine (C), and guanine (G). Each chain of DNA is paired with a "complementary" strand. One is the "sense" strand which is used to make proteins. The other strand is the "antisense" strand which has functions other than making proteins, some of them with therapeutic potential, discussed infra. Each "sense" strand includes sets of three nucleotides, each of which is interpreted, or "read," by cellular machinery to represent a single amino acid. The ordering of the codons determines the sequence of amino acids in the protein. Therefore, the genetic code is a template which guides cells in manufacturing, or "coding for," proteins with an exact sequence of amino acids.

The genetic code has 64 possible combinations (4 nucleotides, taken 3 at a time). [n.7] Because there are only 20 amino acids coded for, there is "redundancy" in the code, with some amino acids being coded for by 6 different codons. Other amino acids are coded for by only a single codon. This fact has both experimental and legal ramifications, discussed infra.

The actual way in which proteins are made is complex. First, DNA is "transcribed" into ribonucleic acid (RNA), another long but single strand of nucleotides that retains the sequence information contained in DNA. Genomic DNA contains not only coding regions, but also non-coding regions interspersed within the gene. These non-coding regions, or "introns," are also transcribed into RNA. The cell's nucleus recognizes introns and removes them, making "messenger" RNA (mRNA). The mRNA is then "read" by cellular machinery that "translates" the mRNA sequence of codons into a protein sequence. This process is known as "expression." Furthermore, after synthesis, the protein takes on its functional form, or "matures," and is stored in the cell or released. This key step, known as "post-translational modification," involves the proper folding necessary for large proteins to hold their functional shape, the modifying of certain amino acids, the adding of sugar groups to selected proteins, and/or the aggregating of individual protein molecules into functional aggregates. The complete protein is released from the cell after all of these steps are finished.

*465 D. cDNA Manufacture Using Biotechnology

The "traditional" approach to making products using biotechnology involves several steps, starting with a genetic template. However, very rarely is the genomic DNA used. Rather, the process relies on the fact that cells normally make large numbers of different

proteins, each of which is translated from a specific mRNA molecule. Thus, the cells make the mRNA, which can be extracted, purified and used to make "complementary" DNA (cDNA), which becomes the "gene" used in biotechnology.

It is important to note that the cDNA obtained in this way is not genomic DNA, but rather is truly "new" in a biological sense. The cDNA is "new" because genomic DNA is comprised of the protein-coding "exons" interspersed with the non-coding "introns," which are usually removed by the RNA processing steps that occur in the nucleus. Protein-coding regions comprise only approximately 2-3% of the DNA in the genome, whereas the non-coding regions comprise 97-98% of the DNA. [n.8]

This biological novelty is one reason for the relatively easy time inventors have had in patenting cDNA. cDNA coding for a normal cellular protein is not "natural," but arises only with the process of reverse transcription of mRNA, which is usually not natural. The only exception are for certain types of viruses which contain RNA and not DNA as their genomic material. These "retroviruses," such as the HIV that causes AIDS, infect cells with their RNA. They then instruct the cell to use a "reverse transcriptase" to turn the RNA into cDNA. The cDNA represents the new genetic material of the infected cells. The most common use of retroviruses in biotechnology is as a source of reverse transcriptase.

The steps used for making cDNA are:

1. Create bacteria that transcribe the mRNA that codes for the protein of interest.
    a. Extract mRNA from cells that are making the protein of interest.
    b. Use reverse transcriptase to create a "library" of cDNA molecules from the mRNA.
    c. Insert these cDNA molecules into viral "vectors."
    d. Infect bacteria in culture with the vectors containing the desired cDNA.

*466 2. Synthesize cDNA "probes" that can recognize the cDNA which codes for the protein of interest.
    a. Identify, isolate and purify the protein of interest.
    b. Determine some of the exact sequence of the protein.
    c. Predict codons which can code for the protein.
    d. Manufacture DNA "probes" complementary to codons predicted for the protein. This step may require making many different probes to account for the redundancy in the genetic code.

3. Identify colonies of bacteria whose DNA "hybridizes" to the probes. These colonies contain cDNA that codes for the protein of interest. Grow large amounts of, or "clone," this specific bacterium, and finally, isolate and purify the cDNA. [n.9]

4. Remove the cDNA from the bacterial vector and insert it into a vector suitable for expression in mammalian cells. This step may or may not be necessary for proper maturation.

E. Protein Manufacture Using Biotechnology

Having isolated a cDNA which codes for a protein of interest, the following steps involve the expression of the cDNA template in an appropriate cell to make the protein of interest:

1. Determine the sequence of the cDNA and ensure that it codes for a protein. Three required elements for protein-coding regions are: a "start" sequence to begin translation, an "open reading frame" [n.10] to correctly code for the protein and a "stop" sequence to cease protein manufacture.

2. Insert the cDNA into cells that can make the protein. The cell type chosen for expression must be capable of not only making the amino acid chain, but also of the "post-translational" modifications necessary for the protein's activity.

3. Finally, once a functional cDNA and expression system have been created, mass production, purification and sales are possible.

*467 II. PATENTING BIOTECHNOLOGY

Because a great deal of money is needed to take advantage of discoveries in biotechnology, and because most money doesn't come directly from the government, private sources of funding are needed. Further, the therapeutic potential of biotechnologically derived products means that there is the possibility of great financial returns to investors. This potential return has led to an explosion of growth in biotechnology companies. Such growth can only continue if financing is predictabile. Venture capital is currently a major source of investment. Predictability in capital investment is fostered by providing certainty of ownership and property rights in the inventions, primarily through the use of patent laws.

A. 35 U.S.C. § 101: Inventions Patentable

1. Patentable Subject Matter

Each of the steps described above may be protectable under the patent laws. Historically, however, the Patent and Trademark Office (PTO) has refused, under the "natural products" doctrine, to issue patents on biological materials. According to the Supreme Court in Funk Bros. Seed Co. v. Kalo Inoculant Co, [n.11] "patents cannot issue for the discovery of the phenomena of nature. They are manifestations of laws of nature, free to all men and reserved exclusively to none. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end." [n.12] In Funk, the application for a patent was on a mixture of naturally occurring bacteria that fix nitrogen. [n.13] Although the mixture was very useful, the Supreme Court denied patentability because only naturally occurring processes led to the value of the mixture. No new properties were created in any of the bacteria. The inventors simply recognized the natural properties of the bacteria and took advantage of them. Therefore, without creating anything "new," the invention was not patentable subject matter under 35 U.S.C. § 101. [n.14]

*468 In contrast with Funk, the case of Diamond v. Chakrabarty [n.15] upheld the patentability of a "new" bacterium containing cDNA sequences not normally found in the same organism. In Diamond, the inventors made cDNAs that coded for four different enzymes, each of which could degrade different types of oil. By putting all of them in a single organism, the inventors created "a non-naturally occurring manufacture or composition of matter - a product of human ingenuity 'having a distinctive name, character and use.'" [n.16]

Moreover, there are important exceptions to the natural products doctrine for materials that, although naturally made, are not naturally present in a form that is "useful" as defined in Title 35. Thus, a naturally occurring material may be prepared in a novel, non-natural form or used in a nonobvious way to render the material patentable. An example that predates modern biotechnology is a patent issued for purified prostaglandin, [n.17] a hormone present in small quantities in most animal tissues. Because of the low concentration in the naturally occurring fluids, the prostaglandin was useless for medical purposes. However, by purifying the material sufficiently to make it useful in treating human disease, the inventors created a form of the material which was sufficiently "new" to allow patentability. [n.18]

Since then, there have been a large number of patents issued for cDNA molecules and purified biomolecules such as proteins. For example, Amgen, Inc. obtained patents on cDNA [n.19] that codes for the red blood cell growth promoting hormone, erythropoietin (EPO), the transformed cell line which produces EPO and the methods for manufacturing EPO using recombinant techniques. Interestingly, the patent on the naturally occurring purified EPO molecule itself issued to a different institution. [n.20] Since Diamond, many recombinant proteins have been patented which have been used extensively to treat various diseases in humans.

The prohibition against patenting natural products does not apply to cDNA because, with the rare exceptions for retroviruses, cDNA does not exist in nature. Further, the naturally occurring retroviral cDNA molecules *469 do not code for any known mammalian protein, but only for certain viral proteins. Therefore, cDNA molecules are easily included within § 101 as patentable subject matter.

To patent these discoveries, applicants must meet three tests: utility, novelty and nonobviousness.

2. Utility

In general, for an invention to have utility, it must actually be able to achieve some desired specific result. [n.21] Thus, inventions that have no known use other than for experimentation are not patentable. [n.22] This principle is important to the consideration of the patentability of cDNAs derived through one strategy used in the human genome projects, discussed infra.

The uses for biotechnologically derived products include symptomatic therapy, genetic reconstitution, and diagnosis. The use of biotechnologically derived proteins in symptomatic therapy is now well-established. For example, Amgen Inc., now has gross sales of approximately $500 million per year for EPO. [n.23] The utility for such a human therapeutic agent need not be demonstrated by tests in people, as anyutility is sufficient if it meets the requirements of Brenner v. Manson. [n.24]

In genetic reconstitution, in contrast to protein technology, the naturally accurring product, genomic DNA itself, even in purified form, is nearly useless for therapeutic purposes. This is because genomic DNA contains introns that interrupt the genetic code and stop the production of proteins. Only by deleting the introns in the transcribed mRNA does genomic DNA become suitable for making proteins. This deletion occurs in the nucleus and only occurs for RNA transcribed there. Further, it is difficult to get large pieces of DNA into cells in vivo without harming the organism. Usual methods for getting DNA into cells in vitro involve osmotic shock, temperature changes, or combining the DNA to large particles, such as plastic beads, and allowing the cells to internalize or "endocytose" them.

*470 New techniques for introducing DNA into cells involve the use of viruses, which can recognize specific cell types, [n.25] or the use of lipid (fatty) particles containing DNA. These tools can allow DNA to be introduced into cells, but the methods are not yet well worked out. Even if it is possible to get genomic DNA into cells, it is not easy to get the DNA into the nucleus, where it can be transcribed into RNA. Therefore, most contemplated therapeutic uses of DNA involve cDNA which is packaged in vectors. cDNA- containing vectors may remain in the cytoplasm of the cell, and regulate the production of their protein-coding regions independently of the cell's nucleus. Furthermore, because the introns have already been removed, transcription of the coding region results in a continuous open reading frame, capable of being translated into protein without any RNA processing.

In addition, DNA sequences are useful for diagnosing certain genetic diseases or traits, such as cystic fibrosis or Tay-Sach's disease. [n.26] There is a large industry based on the ability to determine genotypic variants. These are often very useful in determining lineage issues such as parentage. Additionally, forensic pathologists are now using DNA analysis to identify possible sources of biological materials left at crime scenes. These include blood, saliva, semen, hair and tissue fragments. The actual determination of forensic similarity is not based on sequencing the entire genome, but rather on three different strategies. The first strategy is to determine the probability that DNA fragments of certain lengths would occur in a population compared to the presence of those length fragments obtained at the crime scene. The second strategy is to compare short sequences of DNA within certain variable regions of the genome. The third strategy is to compare the sequences of longer pieces of DNA within mitochondria.

B. 35 U.S.C. § 102: Novelty

To be patentable, the invention must be novel. [n.27] For an application to be denied as anticipated under this section, the prior art must contain, in a *471 single reference, all the elements of the invention. [n.28] Further, a patent may not be denied as anticipated unless all elements of the claimed invention are disclosed in a single prior art reference. [n.29] Novelty is usually not a significant stumbling block to patentability, especially if the inventor can clearly define the invention as different from the prior art. [n.30] One exception is for a protein obtained by biochemical purification, which can anticipate the same protein made by recombinant methods. [n.31] In such cases, the existence of a composition of matter patent for a naturally occurring protein that cannot be produced in large quantities can have a stifling effect on the production of the same protein by recombinant means, thus decreasing the amount of protein available for therapeutic uses. This appears to run counter to the Constitutional intent of the patent law to "promote the Progress of Science and useful Arts." [n.32]

As a result of such a stifling effect on composition of matter claims, there is an increasing reliance on product-by-process claims, which define the end product by its method of manufacture. Such process patents have recently been allowed in the semiconductor industry by the Patent Process Amendment Act of 1988. [n.33] Although this amendment does not specifically apply to the chemical and biotechnological areas yet, legislation is under consideration to protect process claims from foreign infringers who manufacture products using biotechnological methods and then import those products into the United States, discussed infra.

*472 Some recombinant proteins are truly novel, having unique characteristics suited to specific therapeutic needs. For example, an enzyme known as neutral endopeptidase (NEP) is a very large, membrane-bound enzyme that digests certain disease-causing proteins. [n.34] By degrading these deleterious proteins, this enzyme may be useful in treating certain inflammatory diseases such as asthma and dermatitis. However, because of its large size and because it sticks to membranes, NEP may be difficult to deliver to the site of the disease. Not only does the NEP stick to membranes, it sticks to itself, resulting in very large clumps of protein which do not easily diffuse outside the blood stream. To circumvent this problem, genetic engineering has been used to make a protein that is lacking in that "sticky" part. [n.35] Thus, the engineered protein is readily soluble in water and doesn't clump. This new protein has never occurred in nature, and was therefore found to be novel and patentable by the PTO. [n.36] Currently, many scientists and companies are modifying naturally occurring molecules for specific purposes.

C. 35 USC § 103: Nonobviousness

To be patentable, an invention must be also be nonobvious. [n.37] In biotechnology, the argument may be made that once a protein is discovered, the need is obvious for its isolation, purification, and sequencing. Further, once that is done, making a cDNA molecule, transfecting a cell line and expressing the recombinant protein may also be obvious. In fact, section 103 rejections of biotechnological inventions by the PTO have been some of the most difficult to overcome. However, at least historically,

accomplishing these steps has required ingenuity, skill and luck. Prior to the late 1980s, most of these steps were fraught with uncertainty, and the outcome was not guaranteed. Thus, many cDNA cloning projects were *473 abandoned. But, some of them resulted in success, such as the approach taken by Amgen to clone the cDNA for EPO. [n.38]

The issue of whether or not a specific cDNA is nonobvious is complex. On the one hand, if a cDNA codes for a newly discovered protein, then it is most likely to be held nonobvious. However, the cDNA coding for an already well- known and characterized protein is less likely to be considered nonobvious. Recently, the technology has improved to the point where now, even with only a small portion of a protein's sequence, the corresponding cDNA can be created and its sequence determined rapidly in a few weeks. Only a few additional weeks may be needed to use the cDNA to express proteins. In fact, some people have suggested that DNA technology is now so routine as to make obvious certain inventions that as recently as 10 years ago were considered nonobvious. This apparent change in the standard for patentability occurred because the finding of nonobviousness is a function of, among other things, the skill in the relevant art at the time of the invention. [n.39] As the skill in the art improves, prior nonobvious strategies become well known and widely used, and therefore become obvious.

One nonobvious strategy is to rely on a non-naturally occurring DNA sequence which can code for a particular protein, not necessarily the sequence which does so naturally. Because of the redundancy of the genetic code, there are approximately 1036 different DNA sequences which can code for an average sized protein. Very few of these are naturally-occurring sequences. The determination of nonobviousness may therefore be due not to the amino acid sequence, but rather to practical concerns involved in making cDNA that can be successfully expressed.

One such practical necessity is the need to be able to remove, or "restrict," the sequence for transfer into other bacterial or viral organisms. Highly "DNA- sequence specific" restriction endonucleases are used for this purpose. Because there may be no convenient restriction site at the ends of the natural coding sequence, the creation, or "genetic engineering," of such sites by varying the genetic code of the cDNA may be necessary. Redundant codes for specific amino acids are selected for their ability to be recognized by restriction endonucleases. As long as the resulting cDNA *474 codes for the correct amino acid sequence, the cDNA will be useful to make the protein. Because exactly where and how to make these restriction sites may not be readily apparent, nonobviousness may be shown.

Another significant issue is whether differences in the post- translation processing affect patentability. For example, because of a lack of glycosylation, NEP, a mammalian protein, cannot be made in functional form by bacteria. [n.40] Whether this distinction makes any difference to patentability was the issue raised in Ex Parte Aggarwal, [n.41] where glycosylated forms of lymphotoxin were prepared in mammalian and yeast cells, and non-glycosylated forms were made in bacterial cells. The discovery was that non-naturally occurring, non-glycosylated lymphotoxin had anti-tumor effects in vivo, thus providing therapeutic utility. The PTO rejected this claim as obvious under the prior art

that showed that glycosylated lymphotoxin produced in mammalian cells had anti-tumor effect. However, the Patent and Trademark Office Board of Patent Appeals and Interferences held that the non-glycosylated form's anti-tumor activity was not expected, solely based on the presence of activity of the glycosylated forms, and therefore was nonobvious. [n.42] A fair conclusion is that such distinctions based on post-translation processing must be determined on a case-by-case basis.

The nonobviousness of a product may also flow from using nonobvious methods. In the controversial case of Amgen v. Chugai Pharmaceuticals, [n.43] the discoverers of the natural cDNA sequence for human EPO used 250 probes, each with a slightly different sequence based on the redundancy of the genetic code. Obviously, it is much easier to make 250 probes than 10%r36! However, even though the task was easier than making all possible probes for EPO, the work which preceded and followed the successful isolation of the cDNA sequence for this protein was very difficult. As with all fields, as the ordinary skill in the art improves, more new inventions will be considered obvious, and thus, not patentable.

*475 III. ALTERNATIVE APPROACH TO BIOTECHNOLOGY: THE HUMAN GENOME PROJECTS

Many patents for products derived from the human genome have already issued, and some of these products have been made for sale. The Human Genome Projects are a logical extension of this strategy, but it specifically targets projects with centralized organization and common goals. The projects originated in the mid-1980s through the efforts of, among others, Robert Sinsheimer and Charles DeLisi, who believed that it would be possible to reveal genetic mutations by comparing a child's DNA with that of his or her parents' DNA, base pair by base pair. [n.44] Many different actual projects are underway, and include specific searches for disease genes such as those responsible for Huntington's disease and colonic cancer. [n.45] Additionally, another type of project, based on a "structural" approach, aims at determining only certain randomly selected sequences of human DNA. This type of project is made possible by recent advances in sequencing technology, [n.46] and has resulted in a great deal of sequence information without accompanying information about the location of the sequences, or their function. This experimental strategy has created the need to re-examine the legal aspects of patentability of these types of inventions.

A. Aims Of The Human Genome Projects

The first major aim of the projects is to provide medical and biological science with the sequence of the human genome. [n.47] "The immediate goal of genome projects is not complete understanding, but creating tools to bring about such understanding . . . ." [n.48] Given the proven therapeutic potential of biotechnologically derived medicines, this information is certainly valuable. However, sequencing the entire genome is a huge task because each person's genome contains an estimated 3 billion base pairs of DNA. [n.49]

This includes between 100,000 and 300,000 genes, each of which codes for a different protein. The DNA coding for each gene varies in length from 10,000 base pairs for small proteins to over 300,000 base pairs for the *476 largest ones. [n.50] In addition to sequence information, other aims of the Human Genome Projects include the establishment of databases containing cDNA sequence information and the function of identified genes, generation of maps of human chromosomes, creation of repositories of human chromosomal DNA, development of new methods for analyzing DNA, and study of DNA sequences from other organisms. [n.51]

Although the latter are legitimate aims, determining the entire sequence of the human genome, is paramount. This goal's importance has been primarily due to the recent advances in DNA sequencing technology, [n.52] which permits automated cDNA sequencing with the capacity to sequence thousands of cDNAs per year. [n.53]

Although there was sufficient interest in the aims of the Projects to result in funding by Congress, there are a number of new issues raised concerning acquiring, using, and exploiting the information obtained.

B. Ownership Of Human Genome Sequence Information

Of these issues, perhaps none is as divisive as the controversy over the potential ownership of the results of the Human Genome Projects. As long as the genome was being sequenced slowly, protein by protein, using the traditional biotechnological approach, the ownership of the cDNA sequence was not paramount in the public debate. However, with the possibility of the entire genome being sequenced rapidly, by only a few organizations for profit, the controversy has taken on new dimensions. Many believe that our genes belong to everyone. [n.54] In contrast, some in the biotechnology industry are very interested in claiming ownership rights to this sequence information.

Acquisition of intellectual property rights in cDNA sequences may be justified as an incentive to undertake costly research and development. Certainly, vast amounts of money are required to develop treatments for diseases. Biotechnological therapies are especially expensive. Developing a new drug may cost as much as $231 million and may take up to 12 years to accomplish. [n.55] Few private concerns are likely to be willing to spend such vast sums on a project without some certainty that they would own *477 the products and patent rights that result from the work. Without ownership of these rights, there would be no incentive to spend a lot of money because the ability to recapture the investment would be limited. In fact, in one opinion, approximately 60% of pharmaceutical products would not have been developed and produced had there not been patent protection for the inventions. [n.56] Thus, a central issue of the Human Genome Projects is to define ownership rights in the sequence of human DNA and the products derived from them.

C. The NIH Patent Application For Expressed Sequence Tags (ESTs)

The ownership controversy became widespread among scientists and lawyers alike with the filing of a patent application in 1991 by the National Institutes of Health (NIH), followed later by applications by several private companies for patent protection on partial sequences of cDNA, called expressed sequence tags, or "ESTs." [n.57]

The patent application for ESTs is based on a different approach from the one discussed above for determining the cDNA sequence coding for a known protein. The new strategy begins with the creation of a library of cDNAs as discussed above. Such a library contains a large number of short cDNA sequences, made by reverse transcription, representing pieces of all of the mRNAs made by the cell. Most of the sequences code for unknown or at least unidentified proteins. Furthermore, with few exceptions, the locations of the cDNA sequences within the genome are not known, making their further study very difficult. Finally, and possibly the most disturbing feature from a patentability and development perspective, is the fact that the ESTs are almost never complete and cannot code for a complete, functional protein. In spite of these drawbacks, the discoverer of the ESTs, Dr. Craig Venter, believed at the time that this strategy was needed because it afforded the possibility of obtaining sequence information at much less expense relative to conventional means. [n.58]

The NIH and some members of the biotechnology industry were very interested in patenting the discoveries. By virtue of the ability to sequence huge numbers of cDNA molecules, many believe that ownership of the sequence information can provide a competitive advantage in the *478 development of new drugs using biotechnology. Ownership of ESTs could provide an advantage over competitors if such sequences anticipate, or make obvious, the work of subsequent scientists who clone entire genes and express proteins. Such anticipation, it is argued, would preempt the field of biotechnology for those who have the EST-sequencing technology. [n.59] Further, because the traditional methods are labor, time, and capital intensive, being able to use the rapid sequencing technology would provide a great business advantage and, it is argued, might also allow rapid medical advances.

There were two primary motives for filing the NIH application. First, as suggested by Reid G. Adler, head of the Technology Transfer Division at the NIH, was the concern that publication without patenting of even the partial sequences of the ESTs would be sufficient prior art to make the patentability of the full length cDNA impossible because of lack of nonobviousness. [n.60] The rationale has merit because even short (200 - 500 base pairs) pieces of DNA are likely to be sufficiently unique to belong to only a single gene. Therefore, given the partial sequence, using the sequence to probe for the full length cDNA would be obvious. The second rationale was that by patenting the ESTs, the NIH could ensure that anyone who wanted them could obtain them through a non-exclusive license. According to Adler, "Our concern was to protect the invention early enough to give meaningful patent protection to the companies that might seek a license from NIH." [n.61] However, the NIH policy of providing non-exclusive licenses is unlikely to provide enough security to ensure capital investment.

Therefore, even if patented, the NIH's ESTs may not be used to develop products.

Thus, with the advent of rapid sequencing techniques, a new series of controversies grew. The controversies have colored the debate regarding the NIH application, and even now, after the NIH's decision to withdraw the application, [n.62] the controversies persist.

*479 IV. PATENTABILITY OF THE HUMAN GENOME PROJECTS

This section discusses the patentability of ESTs and other short pieces of cDNA of unknown function. The PTO has rejected the NIH application, relying upon analysis of each of the major sections defining requirements of patentability for lack of utility, anticipation, lack of nonobviousness, and inadequate disclosure. This section is organized sequentially according to the patent code.

A. 35 U.S.C. § 101: Inventions Patentable

1. Patentable Subject Matter

As already discussed, cDNAs have been held patentable subject matter if other requirements of patentability are met. It is important to acknowledge that the EST project seeks only to identify cDNA sequences, without necessarily knowing whether they code for a protein, and even if they do, what the proteins are or what they do.

These issues are significant in determining the degree of protection which should be available to companies and scientists. Since the germinal case of Diamond v. Chakrabarty, [n.63] which held for the first time that a biological organism may be patented, there have been many patents issued on biotechnological products, including DNA sequences, recombinantly expressed proteins, and the cell cultures that produce the proteins. Because determination of cDNA sequence information may require invention and because cDNA is not naturally occurring, ESTs are not necessarily unpatentable, as discussed supra. However, other requirements of the Patent Act may raise serious questions about patentability of the fruits of the Human Genome Projects.

2. Utility

The next issue is whether ESTs meet the criterion for utility as required by the Patent Act. The most recent guidance from the Supreme Court is in their decision in Brenner v. Manson, [n.64] in which a patent application for a pharmaceutical compound was denied because the product claimed, although new and nonobvious, had no known use. The use claimed was that the compound was structurally similar to compounds with known anti-*480 tumor effects, and was therefore likely to possess such effects themselves. Such effects could be tested by further experimentation. However, the Supreme Court denied

patentability because "a useful invention is one which may be applied to a beneficial use in society . . . and is not frivolous and insignificant." Further, " a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." Moreover, to be patentable, a compound must have "substantial utility," or "confer a specific benefit . . . in its currently available form," [n.65] Given the unpredictability about pharmacological effects of drugs, the utility of known analogs does not transfer to unknown compounds.

The PTO had previously rejected applications on the theory that if the prior art raised a question and provided a general strategy for solving the question, then the subsequent invention was unpatentable as being "obvious to try." Such a standard would require that each invention must arise de novo from the inventor's mind. This standard apparently ignores the truism that scientific progress is nearly always incremental. Rarely is an invention so new that no one had never considered it before. An analogy might be to require such nonobviousness and novelty as is worthy of Nobel Prizes to be the standard of patentability. However, such a high standard would provide little incentive to invent. Fortunately, the Court of Appeals for the Federal Circuit (CAFC) recently rejected the PTO's proposed standard. [n.66] Relying on the reasoning of Brenner, the CAFC rejected an "obvious to experiment" standard offered by the PTO. [n.67] Therefore, according to the Court, some real utility is needed. However, it is now generally accepted that " a small degree of utility is sufficient. The claimed invention must be capable of performing some beneficial function...." [n.68]

On its face, most ESTs would not make useful proteins, for even if such fragments coded for proteins, they would be incomplete, and the function of the proteins would be unknown. However, there are other uses of ESTs, which may confer patentable utility. Mr. Adler of the NIH [n.69] suggested that *481 ESTs were useful as markers for the chromosomes on which they reside, [n.70] or to identify and clone the entire cDNA of which the fragment is a part. Further uses could include forensic identification of biological material left at crime scenes. Thus, even though the "best" utility might easily be for making therapeutic proteins, the utility described above may be sufficient for patentability under DuPont v. Berkeley and Co. [n.71]

In addition to claiming approximately 2,500 ESTs, the NIH patent application included claims to the entire cDNA sequence corresponding to each EST, as well as the protein coded for by the entire cDNA. The theory is one of "inherency," under which sufficiently unique fragments could be part of only a single complete cDNA gene, and thus, the entire cDNA would therefore be identified uniquely by the fragment. Thus, the argument is that the entire sequence is "inherent" within the sequence of the fragment. Similarly, claims were drawn to include the protein that the entire cDNA would encode. The rationale was that the protein sequence is inherent in the cDNA sequence. However, this strategy has been met with limited success. In the past, the protein was known, and so the DNA and protein were patented separately. No claims on full-length DNA or protein have issued on the basis of a fragment of DNA sequence. Furthermore, the broad claims raise possibly insurmountable problems of the adequacy of disclosure under 35 U.S.C. § 112.

Ultimately, the PTO rejected the claimed utility citing the lack of known demonstrated uses and the lack of guidance for the development of such uses by others. [n.72] These problems may be the greatest hurdles to overcome for this kind of approach. However, there are other hurdles specific to the NIH application.

B. 35 USC § 102: Novelty

Upon discovery of a cDNA sequence, investigators search computer databases to see if the sequence has previously been disclosed. If the *482 sequence is already present, then the sequence is anticipated under 35 U.S.C. § 102 and is not patentable. If the sequence is not disclosed, then it meets the requirements of § 102. For ESTs, anticipation leads to an interesting problem; two different fragments from the same gene may be disclosed by different inventors. Thus, a fragment's sequence may be novel, but the "inherently" disclosed full-length sequence would be anticipated by the prior art. [n.73]

This problem of anticipation, however, was not the focus of the PTO's rejection. Instead, the PTO relied on 35 U.S.C. § 102, holding that the cDNAs were anticipated by their prior use in this country. [n.74] In this case, the PTO noted that Dr. Venter did not create his own cDNA library, but rather purchased it from Stratagene, a company who sells molecular biological supplies. Because this library had been for sale and had been previously used by other purchasers, the cDNAs themselves lacked patentable novelty. The PTO held the sequences to be anticipated in spite of the likely fact that few, if any, of the other investigators who used the library had sequenced it to the same degree as Dr. Venter. However, the PTO could have easily held that once the cDNA library was in hand, the sequence of the pieces was inherent within them. [n.75]

This anticipation problem may be unique to this particular application. Given the relative ease of making new cDNA libraries, other applicants are unlikely to continue to try to patent ESTs from commercially available libraries.

Additionally, although the NIH claimed "enriched" or "purified" full-length sequences by virtue of the "inherent" identification of the gene given a sufficiently long partial sequence, [n.76] the portion of the PTO rejection published in SCIENCE [n.77] did not mention this possibility.

*483 C. 35 USC § 103: Nonobviousness

The PTO rejected many of the NIH claims as being obvious in light of prior art. For example, the PTO compared disclosed EST sequences with those published in prior art and found that one 15 base pair sequence was previously described. [n.78] Other prior art taught how to use such probes. The identity of cDNA sequences meant that it would have been obvious to one of ordinary skill in the art to use the data to construct an oligonucleotide probe that would hybridize to the DNA disclosed by the NIH.

Furthermore, if the PTO were to reject claims for full-length cDNAs based on ESTs, and were to allow patent claims for ESTs, it would create an interesting additional dilemma. Would the patent on ESTs make subsequent patent applications for full length cDNAs obvious under § 103? The answer may be yes! Because the current skill in the art is sufficiently advanced, the use of a unique sequence of cDNA as a probe to identify the full-length cDNA may be obvious. Furthermore, even without patenting ESTs, so long as the sequences were published, the problem could exist.

In an attempt to circumvent this potentially fatal problem, Dr. Venter proposed a statutory solution to amend 35 U.S.C. § 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." [n.79]

Although such a statutory change would obviate this specific problem, such a change raises other troubling issues. First, even though a full-length cDNA would not be legally "obvious" under the new amendment, it would be obvious under the currently accepted meaning of the word and would effectively dilute this requirement of patentability. This could permit patents to issue based on a minimal amount of invention. Because only a few minutes of an automated sequencer's time and only a few dollars are required to sequence an EST, patents would issue for essentially no investment of time, money, or skill in the art. Therefore, there would be little incentive to undertake the truly difficult process of determining the indentity, structure, and functions of the proteins that these cDNAs encode. Such lack of incentive appears to be counter to the purpose of the Patent Act.

Moreover, if a partial cDNA sequence can render the full-length sequence obvious, a partial cDNA sequence might also render the expression of a protein obvious. The state of the current art is such that given a cDNA sequence, a protein may easily be made from it using bacterial or mammalian cell expression systems. If expression of a cDNA is obvious, *484 then there would be no protection for the protein unless a nonobvious, novel method were used. Furthermore, this type of process protection is less frequently granted because of the PTO's perception that expression methods are now so well-known and used that virtually any cDNA can be expressed. [n.80] For reasons discussed above, a given protein may or may not be produced in functional form by a particular cell type in culture. However, the PTO has apparently taken the position that biotechnological processes are not sufficiently uncertain. The rationale might be that if one bacterial cell type doesn't work, trying a different one is obvious. If bacterial cells do not work, trying yeast cells then trying yeast cells may be obvious, and if yeast cells do not work, then trying mammalian cells also may be obvious. Because a certain amount of experimentation is allowable, if "not undue," not every detail of a process must be disclosed to be patentable. [n.81] Although fairly well settled in the chemical arts, [n.82] this issue is has not been addressed in the biotechnological arts. Therefore, the Courts will have to deal with legal challenges to the PTO's patentability standard for nonobviousness of composition of matter claims.

In addition, the PTO routinely rejects process claims if the methods are generally known. In In re Durden, [n.83] the applicants used a novel starting material and a known chemical process to synthesize a novel product. Although both the starting material and final products were novel, the CAFC held that the chemical reduction process used had the identical effect on the novel substrate as prior art demonstrated, and thus the process was held unpatentable as obvious. The Court held the decisions narrowly on the facts of the case, [n.84] but in current practice, the PTO has expanded the rationale to include the much less certain results of biotechnology.Therefore, inconsistent application of the rule of Durden by the PTO has caused problems for the biotechnology industry.

One response applicants have used in an attempt to circumvent misapplication of Durden has been to draft claims as those upheld in In re Pleuddemann. [n.85] In Pleuddemann, claims were drawn not to "methods for making," but "methods for use." [n.86] As discussed above, under 35 U.S.C. § 103, even "minimal" utility is sufficient to confer patentability. Even with *485 such changes in claim drafting, the PTO still believes that the change in claim language does not represent a valid way of circumventing Durden. However, neither Durden nor Pleuddemann are directly on point. A more relevant case is In re Mancy, [n.87] where the Court of Claims and Patent Appeals (CCPA) held that novelty and nonobviousness of a new microbe made the manufacture of an antibiotic nonobvious even though the antibiotic was produced using a standard method. Therefore, the novelty and nonobviousness of the process was conferred by the microbe. A similar situation appears to apply to biotechnological processes relying on living bacteria or cells. As held in Diamond, [n.88] the patentability of the bacterial strain was conferred by the new genes inserted into it. Thus, any new transformed cell used for expression of a cDNA is also patentable under Diamond. Further, because the insertion of new genes into strains of cells has unpredictable outcomes, such strains should also be nonobvious. However, the PTO does not follow either this logic nor that of Mancy and continues to reject biotechnology process patent applications under Durden. [n.89]

The problems with process claims as described may have significant detrimental effects on the U.S. biotechnology industry. For example, in Amgen, no process claims for manufacturing recombinant EPO (rEPO) were allowed. Amgen is permitted to sell rEPO in the United States pursuant to FDA approval for treatment of patients with rare diseases. Therefore, even though Amgen holds the patent for the cDNA which codes for EPO, it cannot prevent Chugai Pharmaceuticals from producing rEPO in Japan and then importing that rEPO into the United States. [n.90] As a result, even though Amgen owns the patent to the cDNA, it cannot find a remedy against offshore infringers and stands to lose its market share of rEPO sales once the seven year period of protection expires. [n.91]

In response to this inequity, the Senate passed the Biotechnology Patent Protection Act of 1993 [n.92] by which Title I appends language to *486 35 U.S.C. § 103 which permits biotechnological process patents to be granted if the composition of matter is novel. Thus, for biotechnological inventions, the intent of this legislation is to directly overrule Durden. The House of Representatives passed a similar bill, H.R. 4309, which would

provide non-industry specific protection for process patents. House-Senate resolution of differences between these two bills has yet to occur. The 103rd Congress adjourned without resolving the conflict, but the bills will likely be re- introduced in the 104th Congress.

Further, Title II of the 1993 Act would append language to 35 U.S.C. § 271 to provide liability for infringers of biotechnology patents who import biotechnological products. [n.93] Thus, this provision would explicitly outlaw *487 the actions of foreign corporations to import recombinantly manufactured protiens made by patented processes.

These proposals conform the protection of biotechnological arts to that of the mechanical arts as amended in the Process Patent Act of 1988, which was intended to protect the semiconductor industry. Thus, under the proposed amendments, two of the most economically viable industries in the United States would be afforded greater patent protection.

D. 35 U.S.C. § 112: Enablement

The Patent Law requires that the invention be disclosed sufficiently to enable those skilled in the art to practice the invention. [n.94] But what if the disclosure is for the EST and the claims of the application are drawn to the full-length cDNA or to the protein? Put another way, does the disclosure of a partial sequence enable the full-length cDNA under § 112? According to the inherency argument discussed above, once the EST is known, the full-length sequence may be arguably "inherently disclosed" sufficiently to confer patentability. This idea has some support in case law, [n.95] where a disclosure of a method for making monoclonal antibodies was adequate even though a large amount of labor-intensive laboratory work would be needed to "make or use" the invention. By analogy, given the disclosure of a very long "probe" for DNA, it might take relatively little effort to isolate the complete sequence given the sequence of an EST.

However, even if an EST uniquely identifies a full-length cDNA, by not being explicitly disclosed, such cDNA is not actually placed in the hands of the public. Thus, broad claims are unlikely to issue because the quid pro quo of full disclosure in exchange for patent rights is questionable.

Furthermore, if the rationale of Hybritech and the inherency arguments are accepted, an unanticipated side effect of unknowing infringement could occur. For example, two different ESTs could be found that happen to be part of the same gene. If both are novel, then patents might issue for each. Subsequently, when someone actually isolates the full-length cDNA from one, they will discover that the other "unknown" EST is actually part of the isolated gene. Such a potential problem would seem to be sufficient grounds for rejecting claims drawn to full-length cDNAs based upon disclosure of ESTs. Certainly, as more ESTs are disclosed this problem *488 will arise. If each gene contains approximately 5,000 base pairs, and if ESTs are approximately 500 base pairs in length, then there are 10 non-overlapping ESTs per gene. Therefore, there is an increasing

likelihood that multiple ESTs for single genes will be disclosed. As a result, there may be sufficient rationale for rejecting such applications due to lack of disclosure. Without complete disclosure, it is impossible to teach others in the art exactly what is claimed. Without teaching the scope of the patent, others would not be able to "invent around" the patent. However, neither the PTO nor the Courts have addressed this issue.

Under the recent ruling by the CAFC in Fiers v. Sugano, [n.96] the conception of the entire DNA sequence coding for a protein is necessary to achieve priority for composition of matter claims. In Fiers, the Court held that the act of invention of DNA requires "a definition of that substance other than by its functional utility." [n.97] With only a conception of a use, but without DNA sequence information, at best, the applicant is entitled to product-by-process claims. [n.98]

E. Restriction Requirements

Another interesting problem is likely to arise with applications for ESTs. In a hypothetical application claiming 2,500 cDNA fragments, many of them may be from different genes with potentially many different uses. Therefore, there may be as many as 2,500 different inventions disclosed in the same application. The PTO might assume that there are 2,500 inventions, and therefore, require a separate patent application for each cDNA fragment. However, because some ESTs may represent cDNA from the same gene, a restriction requirement may not necessarily be needed. Unfortunately, there may not be enough information available in an application for multiple ESTs to show that they are all part of the same invention. [n.99] If this ruling stands, the competitive advantage of sequencing cDNA fragments with minimal utility will disappear under a blanket of huge filing and prosecution costs.

In the NIH application however, the PTO did not need to reach these thorny issues. Two grounds under § 112 were sufficient for the PTO's rejection. First, the method used for rapidly sequencing the cDNA fragments had an acknowledged error rate of approximately 3% of the total *489 number of bases sequenced. [n.100] Thus, in a fragment of 300 bases, there is on average 9 bases whose identity are not known with certainty. Further, the positions of the incorrect bases are not known. Therefore, even the fragment claimed is not adequately disclosed. [n.101]

Grounds for rejecting claims to the proteins for which the ESTs code was based on the failure to determine whether the ESTs coded for proteins at all. For example, it is possible that the sequence disclosed is between coding regions, or is located either "upstream" or "downstream" from the coding region. Such upstream or downstream regions may represent either untranslated regulatory regions or "junk" DNA derived from mRNA appended to the coding region. In light of the fact that the applicants couldn't show that the ESTs code for proteins, the disclosure was held to be inadequate.

F. The NIH Abandoned The Application

Although the claims were rejected by the PTO, the NIH had 6 months to respond to the rejection by filing an amendment to the application (which includes a three month extension). However, Dr. Harold Varmus, the new head of the NIH, decided not to pursue the application on multiple ESTs further. [n.102] The decision reversed that of Dr. Varmus' predecessor, Dr. Bernadine Healy, who urged the filing by the NIH in the first place. The decision left open the issues of patentability. The NIH would have been able to press for a rapid appeal through the Patent and Trademark Appeals Board and to the CAFC. However, now such rapid appeal is unlikely.

Dr. Varmus justified the decision to abandon the application based on his belief that "patents on such partial sequences are 'not in the best interests of the public or science.'" [n.103] Given the potential patentability problems discussed, pursuing the new legal grounds would place the NIH at the forefront of patent law, a position that Dr. Varmus believes is inconsistent with the NIH's primary role as a research institution. Thus, the NIH would not be the best advocate of the expansion of patent law necessary to allow issuance of those types of claims. Dr. Varmus' advisers decided that playing such a role didn't justify pursuing the patents. "Although an appeals process by NIH would probably have provided some decision earlier than would have been possible if we had to wait for other applicants, it was unlikely to be a solid or definitive decision." [n.104] Rather, others in the *490 private sector are likely toprosecute such applications with sufficient vigor to resolve such disputes.

In addition to the NIH's decision to abandon this application, the British Medical Council also decided to drop its application for similar fragments of cDNA. [n.105]

V. FUTURE OF BIOTECHNOLOGY AND THE HUMAN GENOME PROJECTS

A. Patenting cDNA Fragments

The fact that the NIH has dropped out of the fight has left commercial companies to prosecute similar claims. There are now several new companies who have filed patents on fragments of DNA. [n.106] Part of the reason why there is continued interest in trying to patent these fragments of DNA, is that few companies are willing to take the risk that if they don't patent the fragments, other competitors may. Recently, Incyte, a California company, filed for several thousand sequences, and Human Genome Sciences (HGS), a Maryland company, filed for several thousand more sequences. As the pace of sequence information increases, it is likely that more applications will follow.

HGS, the company founded by Dr. Craig Venter after he left the NIH, recently announced that it has identified 45,000 ESTs, thus triggering a $12.5 million payment from SmithKline Beecham as part of a $125 million deal signed in 1992. [n.107] Apparently, some companies intend to pursue ESTs as a basis for drug development. However, exactly how Incyte and HGS intend to pursue patent protection is unclear.

Although as of July 1994, HGS has filed at least 25 patent applications, none had then been granted. [n.108] More recently, HGS announced their intent to launch a project aimed at providing non-commercial scientists access to the database of between 30,000 and 35,000 fragments of human cDNA. [n.109] They would set up their own gene bank to provide information solely to nonprofit research groups. HGS and SmithKline would retain commercial rights to potential drugs. The new gene bank would complement the NIH's existing *491 GeneBank which has recently agreed to provide on- line cDNA sequence information in collaboration with Washington University in St. Louis and Merck & Co. [n.110] This collaboration has placed over 50,000 sequences in the gene bank databases which are now in the public domain. The impact on commercialization remains unclear. The fact that some companies have chosen to make sequences public may create pressure on others to disclose their sequences. Furthermore, the Author believes that the Government would support disclosure of information gained as a result of federal funding of the Human Genome Projects.

In addition to the standard cDNA library type of sequencing discussed, Incyte Inc. intends to use new technology to clone the cDNA from single cells, [n.111] and thereby hunt for specific disease genes. Incyte has recently entered an agreement with Pfizer Inc., to provide $25 million, and a similar agreement with Upjohn for non-exclusive licenses to Incyte's database for cDNA sequences. [n.112]

Other companies continue to use a more function-based approach. One such company is Mercator Genetics, Inc., of Menlo Park. According to a spokesperson for Mercator, the major problem with patenting ESTs was one of enablement and disclosure. Mercator's approach is to identify the disease genes directly using positional cloning, a method that does not rely on the identification of any protein. Such an approach was successfully used to clone the genes responsible for cystic fibrosis and Huntington's disease. Even though Mercator's approach does not require a protein, the genes would have utility. Because they derive from individuals with the genetic disorder, such genes are of immediate use in diagnosing the disease in other individuals. Further, because Mercator will sequence the entire gene prior to filing, there will be complete disclosure of the gene. Finally, if the genes have not been previously disclosed, then all of the statutory requirements for patentability will be met.

Even if companies do not obtain patent protection on ESTs, the information is being disseminated. For example, a recent report announced that HGS's search for ESTs has yielded the discovery of a gene which causes colonic cancer. [n.113] This discovery was made possible by collaboration between HGS and researchers from Johns Hopkins School of Medicine. The researchers knew that the gene they were after resembled certain bacterial genes already known. They called HGS asking if any of the *492 ESTs were like those bacterial genes. On the same day, they were able to identify the human gene, and shortly thereafter, they showed that mutants of this gene were responsible for human colon cancer. [n.114] This collaboration represented the first showing that an EST actually had utility under the Patent Act. Since then, another potential product has resulted from EST research. Genentech Inc. recently announced its plans to buy an option on HGS's gene for pulmonary DNAase. [n.115] Genentech currently sells DNAase as a

symptomatic treatment for cystic fibrosis, and believes that a pulmonary-specific DNAase may prove more effective. Thus, even without patent protection, trade secret protection is currently yielding the desired result: namely, the ability to procure license agreements with other biotechnology companies.

B. Patent Term And Publication Reform Act of 1994

Recently, the Senate passed S. 1854, the Patent Term and Publication Reform Act of 1994, [n.116] whose primary aim was to prevent "submarine patents" and to harmonize the United States Patent System with those of other countries, especially Japan. Submarine patents are patents that issue many years (up to 20) after filing, which, when finally granted, may permit their holders to compel retroactive license royalties from a then well-developed field. Although the term of the patent has been extended to 20 years from the date of filing, due to the historically much longer time (up to 60 months after filing) that biotechnology patents must be prosecuted in the PTO before issuance, this change may effectively shorten the effective period of biotechnology patents. For example, if 5 years is required, the effective life of such a biotechnology patent would actually be only 15 years instead of the currently available 17 years.

Furthermore, this problem is relatively unique to biotechnology patents, and thus, the biotechnological arts are likely to suffer for the benefit of the semiconductor industry, which is the primary beneficiary of this amendment. In fact, comments by Mr. Bruce Lehman, the Commissioner *493 of Patents, at a 1994 meeting of the San Francisco Patent and Trademark Law Association suggest that possible changes to the Patent Term Extension Act may counteract the effects of S. 1854. Specifically, the term of a patent may be extended for up to 5 years if delays in implementing the patent are due to governmental regulations. For example, if FDA approval takes the typical period of several years, the patent may be extended to mitigate the lost period of protection. The policy underlying this extension is to provide for sufficient time to allow recovery of capital expenditures needed to develop new drugs. Mr. Lehman suggested that similar extensions might be granted here. This idea was supported in the hearings of the Senate Committee on the Judiciary, Subcommittee on Patents, Copyrights and Trademarks held March 9, 1994. [n.117] One of the witnesses, Professor Harold C. Wegner of the National Law Center of George Washington University acknowledged the disparate effect on biotechnology (up to 60 months to issuance) [n.118] and proposed a solution: "the better approach is to have industry-specific patent extension legislation that balances the interests of the original patent holder with the rights of competitors to enter the marketplace as soon as possible after expiration of the patent term." [n.119] Another possible solution is to have the PTO arrange to have specific industries' patents examined more rapidly, by among other things, allowing U.S. patent examiners to "piggyback" off completed European Patent searches. [n.120]

VI. POLICY ISSUES REGARDING PATENTS ON THE HUMAN GENOME PROJECTS

A. Arguments In Support Of Patenting cDNA Fragments

As outlined in the body of this paper, the primary reason to patent fragments of DNA is to protect the proprietary rights of the inventors. With passage of the Patent Term Amendment Act, [n.121] patent protection will last for 20 years from date of filing. In a field such as biotechnology, patent protection represents a more desirable alternative for the public than trade secret protection. In the absence of patent protection, there is no incentive to disclose genetic information to the public; in fact, there is every incentive to keep such information secret. The incentive to keep cDNA sequence *494 information secret was recently shown by the license arrangements that HGS has reached with Genentech and with SmithKline Beecham. If the genetic fruits of the Human Genome Projects are to be made public, the best way is for patents to be granted. However, ESTs of unknown function have not been patentable for lack of utility.

The lack of patentability raises the question of how the information in ESTs will become public. According to the above analysis, joint ventures between business and academia will likely develop, such as exists between HGS, TIGR, and SmithKline Beecham. ESTs are likely to remain trade secrets until more licenses are negotiated between the sequencing companies and development companies who can use the information directly to develop a product. The Author believes that one of the primary goals of the Human Genome Projects, namely to provide wide public disclosure, may remain unmet until such time as intellectual property protection is afforded this information. Thus, in the short-term, the large expenditure of public money may yield only limited public benefit unless free disclosure for noncommercial use continues.

A possible way to protect ESTs and still make their disclosure public is to create some new form of protection, more like copyright and less like patent protection, possibly like plant patents (35 U.S.C. sec. 161 et seq.) that have relaxed standards for disclosure. [n.122] Such protection would permit public disclosure of the gene sequence information without requiring demonstrated utility, nonobviousness, and without requiring complete disclosure of the entire genes. However, if traditional copyright principles were used, then publication of the entire cDNA sequence would constitute infringement. In exchange for relaxed requirements for patentability, the protection afforded ESTs would be correspondingly less than for other inventions.

B. Arguments Against Patenting cDNA Fragments

One of the most long-range views against patenting cDNA fragments applies to entire cDNA sequences as well. [n.123] According to that commentator, patenting cDNA removes a "tool" of discovery from the public domain and thereby decreases invention. According to this view, patenting cDNA as part of a trend to decrease invention by creating an environment where at each step of biotechnological research, a new patent *495 application is filed. One concern is that if this trend continues, companies will be increasingly focused on protecting inventions with minimal marginal utility over the preceding one, instead of expending resources on invention itself. Thus, this trend as

being contrary to the essence of Brenner v. Manson, [n.124] in which "substantial utility," defined as a "specific benefit in currently available form," was held to be the standard for utility. That commentator would like to see "teeth" put back into the utility requirement under Brenner. He believes that public policy should not provide patent protection for "tools of research" such as DNA, but would permit protection for products actually put into the stream of commerce. Furthermore, the U.S. system should harmonize its system to match the European system to provide "new use" patent protection for previously patented compositions of matter. [n.125] Such policies would, according to this commentator, create additional incentive to develop new uses for old products.

VII. CONCLUSION

The patenting dilemmas presented are examples of legitimate interests in apparent conflict with each another. There is a legitimate desire to sequence the human genome as rapidly as is technologically possible. The recent advances in technology have enabled this desire to be fulfilled with increasing efficiency. Because this aim is linked to the legitimate desire to develop products for human therapy, the need for forging some type of effective protection for the intellectual property rights has led to the premature filing of patent applications. The applications are not necessarily drawn to products in a commercial sense, but may be only tools useful for developing the highest- use commercial products, namely therapeutics. These dilemmas have resulted from disparate demands of scientific pursuit on the one hand, demanding immediate disclosure of all relevant information, and those of commercial pursuit on the other hand, demanding protection of intellectual property before disclosure can be made.

The resolution of the disparate demands is not easy. Given the current requirements for patentability, much of the sequence information resulting from the Human Genome Projects will continue to be protected as trade secrets, and only disclosed as commercial applications become realized. Alternatively, the PTO and the Courts may hold that the interpretation of patent laws can be altered to accommodate the needs of all for protection of *496 cDNA sequence information. However, given the comparative slowness with which these institutions respond to such exigencies, rapid changes in the types of intellectual property protection are unlikely. Therefore, the most likely avenue for remedy will be legislative. With the future passage of the successors to the Biotechnology Patent Protection Act of 1993 and the Patent Term and Publication Reform Act of 1994 by the Senate, there is hope that the patent protection afforded to biotechnology will serve the industry's needs.

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national and international scientific organizations, including a lecture on "Forensic Uses of DNA" at the "Use of DNA Technology in Forensic Sciences" Conference held at the University of San Francisco School of Law in December, 1994. He is a member of several scientific organizations and has served on the editorial board of the American Journal of Physiology. Dr. Borson is an inventor of U.S. Patent 5,262,178 entitled "Therapeutic Use of Enkephalinase."

[n.1]. For an overview of the Human Genome Projects, see generally United States Congress Office of Technology Assessment, Mapping Our Genes: The Human Genome Projects: How Big, How Fast? (1988).

[n.2]. The Human Genome Projects represent a consolidated effort on the part of the Federal Government to determine the structure of the human genome and to make this information available to the public.

[n.3]. Leslie Roberts, Genome Patent Fight Erupts, 254 Sci. 184 Oct. 11, 1991.

[n.4]. See Cohen and Boyer, Construction of Biologically Functional Bacterial Plasmids in vitro, 70 Proc. Nat'l Acad. Sci. 3240 (1973).

[n.5]. U.S. Patent No. 4,237,224, issued December 2, 1980; U.S. Patent No. 4,468,464, issued Aug. 28, 1984; and U.S. Patent No. 4,740,470, issued August 26, 1988.

[n.6]. See generally T. Strachan, The Human Genome, (1992).

[n.7]. Id.

[n.8]. Id. at 8-19.

[n.9]. Rarely does a single cDNA contain the entire sequence needed for protein expression. Usually, many different pieces of cDNA, each of which codes for a part of the protein must be linked together to create the "full-length" sequence, which can be used to express the full-length protein.

[n.10]. The term "open reading frame" refers to a long sequence of codons with no "stop" codons until the final "stop" codon. Random sequences of DNA may contain many

codons, but usually there are several "stop" codons interspersed with coding regions. Such sequences will not be expressed to mature proteins.

[n.11]. 333 U.S. 127 (1948).

[n.12]. Id. at 130.

[n.13]. Id.

[n.14]. 35 U.S.C. § 101 (1988) provides that: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."

[n.15]. 447 U.S. 303 (1980).

[n.16]. Id. at 309-310.

[n.17]. In re Bergstrom, 427 F.2d 1394, 166 U.S.P.Q. 256 (C.C.PA. 1970).

[n.18]. Id. at 1401-1402: The Patent and Trademark Office rejected the application as a product of nature, but the Court of Claims and Patent Appeals held: "by definition, pure materials necessarily differ from less pure or impure materials and, if the latter are the only ones existing and available as a standard of reference . . . perforce the 'pure' materials are 'new' with respect to them."

[n.19]. U.S. Patent No. 4,703,008, issued to Amgen, Inc.

[n.20]. U.S. Patent No. 4,677,195, issued to Genetics Institute, Inc.

[n.21]. Brenner v. Manson, 383 U.S. 519 (1966).

[n.22]. Id.

[n.23]. Senate Committee on the Judiciary, Subcommittee on Patents, Copyrights, and Trademarks, Testimony of Professor Harold C. Wegner, at 8, Mar. 9, 1994. Obtained from Sen. Dennis DiConcini's office.

[n.24]. 383 U.S. 519 (1966) (holding that "substantial utility" is needed); Carter Wallace v. Riverton Laboratories, 433 F.2d. 1034, 167 U.S.P.Q. 656 (Fed. Cir. 1970) (holding that failure to disclose that a new drug was intended primarily as a human therapeutic agent was not a violation of the best mode disclosure requirement). By extension, compliance with the best mode requirement here predisposes that the enablement requirement was fulfilled.

[n.25]. See, e.g., Jean-Michel H. Vos, Herpesviruses as Genetic Vectors, in Human Viruses in Gene Therapy (Jean-Michel H. Vos ed., Carolina Academic Press), reprinted in The Human Genome Projects; Commercial Implications, proceedings of a meeting held Feb. 28 - Mar. 2, 1994. Sponsored by Cambridge Healthtech Institute, Waltham, Mass.

[n.26]. Id.

[n.27]. 35 U.S.C. § 102 (1988) provides, in part, that: "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 patent in the United States . . . ."

[n.28]. Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677, 7 U.S.P.Q.2d 1315, 1316 (Fed. Cir. 1988).

[n.29]. American Seating Co. v. National Seating Co., 586 F.2d 611, 618, 199 U.S.P.Q. 257, 261 (6th Cir. 1978), cert denied., 411 U.S. 907 (1979).

[n.30]. Hormone Research Foundation v. Genentech, Inc., 708 F. Supp. 1096, 1101, 8 U.S.P.Q.2d 1377, 1381 (N.D. Cal. 1988), aff'd in part and vacated in part, 904 F.2d 1558, 15 U.S.P.Q.2d 1039 (Fed. Cir. 1990), cert. denied, 499 U.S. 955 (1991).

[n.31]. E.g., Factor VIII:C is a blood clotting factor present in trace amounts in blood. Genentech, Inc., first produced large amounts of factor VIII:C using recombinant methods. However, the patent for the purified form was issued to Scripps Clinic in 1987. U.S. Reissue Patent No. RE 32,011.

[n.32]. U.S. Const. art. I, § 8, cl. 8.

[n.33]. 35 U.S.C. § 271(g) (1988). This section provides that:

"Whoever without authority imports into the United States or sells or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer . . . ."

That this amendment is directed toward protecting the semiconductor industry is demonstrated by the following:

"A product which is made by a patented process will, for purposes of this title, not be considered to be so made after --

(1) it is materially changed by subsequent processes; or

(2) it becomes a trivial and nonessential component of another product."

[n.34]. D. B. Borson, Roles of Neutral Endopeptidase in Airways, Am. J. Physiology 260 (Lung Cellular and Molecular Physiology 4): L212-L225, 1991. U.S. Patent No. 5,262,178, issued Nov 16, 1993.

[n.35]. D. B. Borson, D. Gies, and C. Gorman, Transmembrane Domain is Necessary for Expression of Functional Human Neutral Endopeptidase, Proc. of the Am. Ass'n for Cell Biology, Boston, Mass. 1991.

[n.36]. U.S. Patent No. 4,960,700.

[n.37]. 35 U.S.C. § 103 (1988) states, in part, that a patent must be denied if: "[T]he 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 pertains."

[n.38]. In the Amgen EPO cloning, scientists synthesized a series of degenerate cDNA probes to screen their libraries for the EPO cDNA. Although they had to use more than 250 such probes, the outcome was successful.

[n.39]. Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966) (Nonobviousness is determined by: (1) scope of the prior art, (2) differences between the prior art and present invention, (3) determination of the level of ordinary skill in the art and (4) secondary, or "objective" factors, such as (a) long-felt need, (b) failure of others, (c) unanticipated results and (d) acquiescence by others).

[n.40]. The amino acid sequence produced by bacteria was correct, but the protein produced is non-functional. Only after expression of the protein in mammalian cells could functional protein be produced.

[n.41]. 23 U.S.P.Q. 1334 (B.P.A.I. 1992).

[n.42]. The PTO's rejection of the patent application was affirmed on other grounds, however.

[n.43]. 927 F.2d 1200, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991), reh'g denied, (1991).

[n.44]. Daniel J. Kevles & Leroy Hood, The Code of Codes, 18, (1992).

[n.45]. See generally, Mapping Our Genes, supra note 1.

[n.46]. Mark D. Adams et al., Complementary DNA Sequencing: Expressed Sequence Tags and Human Genome Projects, 252 Sci. 1651, June 21, 1991.

[n.47]. See generally, Mapping Our Genes, supra note 1.

[n.48]. Id. at 9.

[n.49]. The Human Genome, supra note 6 at 4.

[n.50]. Id.

[n.51]. See generally, Mapping Our Genes, supra note 1.

[n.52]. See Mark Adams et al., supra note 46.

[n.53]. Kevles and Hood, supra note 44, at 313. See also Leslie Roberts, Gambling on a Shortcut to Genome Sequencing, 252 Sci. 1618, June 21, 1991.

[n.54]. H. Curien, The Human Genome Projects and Patents, 254 Sci. 1710, Dec. 20, 1991.

[n.55]. P. R. Vagelos, Are Prescription Drug Prices High?, 252 Sci. 1080, May 24, 1991.

[n.56]. E. Mansfield et al., Rev. Econ. Stat., at 49 (1979), Cited in: Reid G. Adler, Genome Research: Fulfilling the Public's Expectations for Knowledge and Commercialization, 257 Sci. 908, 910, Aug. 14, 1992.

[n.57]. Leslie Roberts, Genome Patent Fight Erupts, 254 Sci. 184, Oct. 11, 1991.

[n.58]. Leslie Roberts, Gambling on a Shortcut to Genome Sequencing, 252 Sci. 1618, June 21, 1991.

[n.59]. Currently most of the rapid sequencers are owned by U.S. institutions.

[n.60]. See supra note 57 at 185.

[n.61]. Id.

[n.62]. NIH Gives up Effort to Patent Pieces of Genes, Wall St. J., Feb. 11, 1994; Christopher Anderson, NIH Drops Bid for Gene Patents, 263 Sci. 909, Feb. 18, 1994.

[n.63]. 447 U.S. 303 (1980).

[n.64]. 383 U.S. 519 (1966).

[n.65]. Id. at 534-35.

[n.66]. In re Dow Chemical, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988). "The PTO presents in essence, an obvious to experiment standard of obviousness."

[n.67]. Id.

[n.68]. E.I. DuPont de Nemours & Co. v. Berkeley & Co., 620 F.2d 1247, 205 U.S.P.Q. 1 (8th Cir. 1980).

[n.69]. Reid G. Adler, Genome Research: Fulfilling the Public's Expectations for Knowledge and Commercialization, 257 Sci. 908, Aug. 14, 1992.

[n.70]. The 1992-1993 catalog from Oncor, Inc. offers for sale a variety of molecular probes which can bind to and "paint" individual chromosomes.

[n.71]. See supra note 68.

[n.72]. Leslie Roberts, Top HSS Lawyer Seeks to Block NIH, 258 Sci. 209, Oct. 9, 1992. "Given what is disclosed in the instant application, it would be necessary for one to do further work in order to establish a utility for any of the nucleotides embraced by the claims. [A]lthough the oligonucleotides embraced by the claims may be hybridized to a variety of different preparations of other nucleic acids, one of skill in the art has no clue as to the significance of any result of such a hybridization because the instant application fails to provide any basis for the interpretation of any putative results."

[n.73]. The argument is that because the ESTs contain sequence information that is likely to be unique (i.e., represents only a single gene) once the sequence of the EST is known, it represents the sequence of a unique gene. Thus, the full-length sequence of the gene is "inherently" known.

[n.74]. 35 U.S.C. § 102(a) (1988) states in part that a patent may be granted unless the claimed invention was known or used by others in this country before the invention thereof by applicant for patent.

[n.75]. The doctrine of inherency states that all the properties of a substance are inherent within it, even if undiscovered. Therefore, if the substance itself is not novel, its properties are similarly not novel.

[n.76]. See supra note 57, at 185.

[n.77]. See supra note 72, at 210.

[n.78]. Id.

[n.79]. Quoted in Pamela A. Docherty, The Human Genome; A Patenting Dilemma. 26 Akron L. Rev. 525-555, 549 (1993).

[n.80]. David Beier and Robert H. Benson, Biotechnology Patent Protection Act, 68 Denv. U. L. Rev. 173-190 (1991).

[n.81]. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

[n.82]. In re Dow Chemical, supra., note 66.

[n.83]. 763 F.2d 1406, 226 U.S.P.Q. 359 (Fed. Cir. 1985).

[n.84]. Id. at 361.

[n.85]. 910 F.2d 823, 15 U.S.P.Q.2d 1738 (Fed. Cir. 1990).

[n.86]. Id., at 827.

[n.87]. 499 F.2d 1289, 182 U.S.P.Q. 303 (C.C.P.A. 1974).

[n.88]. 477 U.S. 303 (1980).

[n.89]. See Beier and Benson, supra note 80, at 177.

[n.90]. Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991), reh'g denied (1991).

[n.91]. Amgen's exclusive rights to sell rEPO in the United States is not due to its patent; rather it is due to Federal Food, Drug, and Cosmetic Act regulation (21 U.S.C. § 360 et. seq. 1988) permitting exclusivity for seven years if the drug is proven safe and effective, and has a target population of less than 200,000.

[n.92]. Title I-Biotechnological Material Patents, 103d Congress, 1st Session, 1993. Senate Bill S-298 significantly amends title 35 U.S.C. § 103 by adding new subsections as follows:

(c) Notwithstanding any other provision of this section, a claimed process of making or using a medicine, manufacture, or composition of matter is not obvious under this section if-

(1) the machine, manufacture, or composition of matter is novel under § 102 of this title and nonobvious under this section;

(2) the claimed process is a biotechnological process as defined in subsection (d); and

(3)(A) the machine, manufacture, or composition of matter, and the claimed process invention at the time it was made, were owned by the same person or subject to an obligation of assignment to the same person; and

(B) claims to the process and to the machine, manufacture, or composition of matter-

(I) are entitled to the same effective filing date; and

(ii) appear in the same patent application, different patent applications, or patent which is owned by the same person and which expires or is set to expire on the same date.

(d) For purposes of this section, the term 'biotechnological process' means any method of making or using living organisms, or parts thereof, for the purpose of making or modifying products. Such term includes recombinant DNA, recombinant RNA, and other processes involving site specific manipulation of genetic material.

S-298 also would amend 35 U.S.C. § 282 by adding:

"A claim issued under the provisions of section 103(c) of this title on a process of making or using a machine, manufacture, or composition of matter shall not be held invalid under section 103 of this title solely because the machine, manufacture, or composition of matter is described to lack novelty under section 102 of this title or to be obvious under section 103 of this title.

[n.93]. Title II-Biotechnological Material Patents, 103d Congress, 1st Session, (1993), amends title 35 U.S.C. § 271 by adding the following new subsection:

(h) Whoever without authority imports into the Unites States or sells or uses within the United States a product which is made by using a biotechnological material (as defined under section 154(b)) which is patented in the United States shall be liable as an infringer if the importation, sale, or use of the product occurs during the term of such patent . . . .

[n.94]. 35 U.S.C. § 112 (1988) provides: "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."

[n.95]. See Hybritech, supra note 81.

[n.96]. 984 F.2d 1164, 25 U.S.P.Q.2d 1601 (Fed. Cir. 1993).

[n.97]. Id. at 1604.

[n.98]. Id. at 1605.

[n.99]. Such restriction requirements have not been needed for applications directed to a finite number of cDNA fragments used to diagnose a single disease or gene.

[n.100]. Leslie Roberts, 258 Sci. 209, 210, Oct. 9, 1992.

[n.101]. 35 U.S.C. § 112 requires that a "full and complete disclosure" of the invention be made.

[n.102]. NIH Gives Up Effort To Patent Pieces of Genes, supra note 62; Anderson, supra note 62.

[n.103]. Christopher Anderson, NIH Drops Bid for Gene Patents, 263 Sci. 909, Feb. 18, 1994.

[n.104]. Id. at 910.

[n.105]. Id.

[n.106]. Christopher Anderson, Genome Project Goes Commercial, 259 Sci. 300, 301, Jan. 15, 1993.

[n.107]. Lisa Piercey, Human Genome Signs Pact To Establish cDNA Database, 5 BioWorld Today, 2, July 7, 1994.

[n.108]. Id.

[n.109]. Charles Craig, Human Genome, TIGR, SmithKline Broadening Access To Gene Sequencing Data. 5 BioWorld Today, 1, Oct 4, 1994.

[n.110]. Id.

[n.111]. Philippa Maister, Incyte, Layton Team To Speed Gene Sequencing, 5 BioWorld Today, April 24, 1994, at 1.

[n.112]. Charles Craig, Incyte, Pfizer Ink Unique Pact Worth $25 M, 5 BioWorld Today, June 24, 1994, at 1.

[n.113]. Wall St. J., March 18, 1994, at B4.

[n.114]. Id.

[n.115]. Philippa Maister, Genetech Buys an Option on Human Genome Gene, 5 BioWorld Today, April 21, 1994, at 1. DNAase is used to breakdown the sticky mucus plugs that are the leading cause of death in patients with cystic fibrosis, a genetic disease. Because DNA is a very long molecule, it is very viscous and is removed from the lungs only with great difficulty. So, therapy with DNAase shortens the strands, making them easier to cough up.

[n.116]. 103d Congress, 2d Session, appends to 35 U.S.C. § 100, language which changes the term of a patent from 17 years from the date of issuance to 20 years from the date of filing. In exchange for this concession by the United States, the Japanese Patent Office will now accept patents in the English language.

[n.117]. Report No 103-82, Biotechnology Patent Protection Act of 1993, furnished by the office of Senator Dennis DiConcini.

[n.118]. Id. Professor Wegner's Senate Testimony.

[n.119]. Id., at 5.

[n.120]. Id., at 13.

[n.121]. 35 U.S.C. § 101, 103d Congress, 2d Session.

[n.122]. 35 U.S.C. sec. 162 provides that: "No plant patent shall be declared invalid for noncompliance with section 112 of this title if the description is as complete as is reasonably possible."

[n.123]. Thomas D. Kiley, Patents on Random Complementary DNA Fragments, 257 Sci. 915, Aug. 14, 1992.

[n.124]. 383 U.S. 535 (1966).

[n.125]. See, supra note 123, at 918.