

THE HUMAN GENOME PROJECT AND PATENTING DNA SEQUENCES

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*The final report will include several appendixes, such as a list of acronyms, a glossary, acknowledgements, methodologies, lists of contract papers and workshops, and an index. Additionally, a copy editor will review the manuscript, photos will be added, and references will be converted to numbers, based on an alpha list for each chapter.

**Also printed as a separate document, with a bibliography of selected references from the full report that might be of interest, as well as available, to the general reader.

CHAPTER 1

SUMMARY AND CONGRESSIONAL OPTIONS

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It is the role of Congress, not this Court, to broaden or narrow the reach of the patent laws. This is especially true where . . . the composition sought to be patented uniquely implicates matters of public concern.

Justice William Brennan
Diamond v. Chakrabarty (1980)

As the 21st century approaches, Congress and the executive branch have committed to funding scientific research and technological developments to determine the location of all human genes. Scientists around the world have undertaken the Human Genome Project--an estimated 15-year, \$3 billion initiative--with the expectation that it will both advance basic knowledge, as well as improve genetic diagnoses and enhance therapies.

Against the backdrop of this scientific effort, comes the realization that intellectual property law, which provides an exclusive property interest in the work of the mind, is of increasing importance to parties conducting genome research. Beginning in summer 1991 and through the next several months, the National Institutes of Health (NIH) applied for patents on thousands of human DNA sequences believed to represent approximately 5 percent of all human genes (box 1-A).

Reaction to the NIH application was swift and largely negative, both in the United States and abroad. NIH's action sparked widespread debate about the legal issues related to patentability, ethical considerations of patenting human DNA sequences, implications for research and development, and economic issues of technology transfer. In many respects, the ensuing discussion reflected existing questions about the commercialization of biomedical research, but was magnified because of the NIH move's scope and breadth.

Concern about the ethical, social, legal, economic, and scientific implications of intellectual property protection and the Human Genome Project led Senator Edward M. Kennedy, Chairman, Committee on Labor and Human Resources; Senator Mark O. Hatfield, Ranking Minority Member, Committee on Appropriations; and Senator Dennis DeConcini, Chairman, Subcommittee on Patents,

Copyrights, and Trademarks, Committee on the Judiciary to request this Office of Technology Assessment (OTA) report. The request also reflects longstanding congressional interest in genetics and biotechnology (table 1-1). And, though NIH abandoned its application in February 1994, intellectual property protection, specifically--and ethical, legal, and social issues (ELSI), generally--of the Human Genome Project remain public policy issues: Since funding the Human Genome Project, Congress has appropriated more than \$21 million to NIH and the U.S. Department of Energy's (DOE) for extramural grants to study the ethical, legal, and social ramifications of the Human Genome Project.

This report focuses on issues arising from patenting human DNA sequences and does not analyze the potential impact of patenting nonhuman DNA sequences--though some of the issues apply generically in considering intellectual property protection of DNA from other sources. Nevertheless, several aspects differ--e.g., ethical considerations of patenting plant or animal DNA--and exploring such differences was not possible for this assessment. Also beyond the scope of this report is an evaluation of the Human Genome Project per se and the use of information derived from it; OTA has analyzed applications of genome research elsewhere.

WHY PATENT DNA?

Molecular biological research and the industrial sector it spawned, biotechnology, is likely to be the principal scientific driving force for the discovery of new drugs as we enter the 21st century. The potential impact of molecular genetics on the discovery of new therapeutic entities significant. Still, human DNA sequence patents clearly had been granted prior to the NIH application (table 1-2 (pending)). Why did controversy arise and who are the stakeholders?

What Is DNA?

DNA, or deoxyribonucleic acid, is a chemical molecule that serves as the repository of genetic information in most living organisms. Through DNA, heritable information is passed from generation to generation. Its structure resembles a twisted ladder, referred to as a double helix (figure 1-1) and consists, in part, of four chemical subunits commonly called bases. These four bases--guanine (G), adenine (A), thymine (T), and cytosine (C)--are the genetic alphabet. The bases pair predictably--A with T, and G with C--to form the double helix structure, and scientists refer to each pairing as a base pair, which also serves as a measurement unit to size DNA fragments.

The unique linear order of bases--i.e., the sequence--in the DNA helix serves as the blueprint for an organism. Put differently, the sequence of bases distinguishes one segment of DNA from another, and any function that can be assigned to a particular stretch of DNA derives from the precise order of bases. Changes, or mutations, in DNA sequences can lead to genetic disease.

The bridge between DNA's chemical information and physical realization of its instructions consists of steps that convert the DNA code into biological products. Through a process called gene expression, a DNA sequence for a structural gene ultimately results in formation of a molecule called a protein (figure 1-2). Proteins are required for the structure, function, and regulation of all cells, tissues, and organs in the body.

Lengths of DNA ranging from fewer than 1,000 to 2 million base pairs comprise a gene, and the DNA sequence determines the composition and nature of the protein product. About 50,000 to 100,000 structural genes--i.e., DNA stretches encoding protein products--are scattered among a matrix of DNA bases that do not encode a protein. In total, over 3.3 billion base pairs constitute the human genome.

Scientists can isolate segments of DNA and determine the sequence of bases. Knowing the order of the bases does not necessarily equate with knowledge of the DNA segment's in vivo function. Conversely, knowing only a fragment of a gene sequence can provide scientists with enough information to assign a putative role in vivo. A DNA sequence need not code for a gene product to be useful commercially or in research; the order of bases in and of itself can be valuable. Unique stretches of DNA sequences can serve as markers for disease genes, and hence be used as a diagnostic tool. Other fragments, for which scientists can only speculate about an in vivo function, are useful for paternity or forensic identification.

What is a Patent?

A patent gives the patent owner a temporary right to exclude all others from making, using, or selling an invention during the term of the patent. Governments grant patents--which have a legal foundation in 15th century Venetian law--under the premise that patents induce inventors to contribute something useful to society by providing the incentive of exclusivity in exchange for public disclosure of the invention. The moral justification of a patent system centers on a social contract between an inventor and society: Society has access to the creative endeavors of inventors, and inventors receive the sole right to develop and use the invention as an inducement and reward for his or her contribution.

In the United States, the Patent and Trademark Office (PTO) of the U.S. Department of Commerce, makes the initial judgment to approve or deny a patent, and U.S. statute dictates that an inventor must clear three principal barriers before PTO grants enforceable patent rights: utility, nonobviousness, and novelty. Valid patents also require a written description of the invention, an enabling disclosure that describes to a person similarly skilled in the art how to make and use the invention, a description of the best mode for carrying out the invention, and claims that recite the protectable invention.

A patent may issue to anyone who invents or discovers a new and useful process, machine, manufacture, or composition of matter, or a new and useful improvement thereof. A patent, however, is not a license for its owner to make, use, or sell the invention. The use of patented products, like the use of other kinds of property, may be regulated by Federal, state, or local law. Differences exist among nations regarding intellectual property protection of inventions, including what constitutes patentable subject matter. U.S. patent law is the broadest and most inventor-friendly statute in the world.

The rationale behind patent law is simple: To foster and reward innovation, the Federal Government guarantees inventors a temporary monopoly on their inventions to justify the risks of development, and so they can pursue a profit. In return the patent holder discloses how the invention works so that the knowledge is available to the public for others to build on.

Principal Elements of a Patentable Invention

Utility ensures that the applicant proposes at least one practical use for an invention, and the utility described in a patent application does not limit the permissible scope of patent claims. However, merely furthering basic research does not suffice to meet the utility criterion: The U.S. Supreme Court rejected the notion that a chemical compound could be patented merely because it could serve as the subject of further investigation.

An inventor also must claim something new to receive a patent. This provision requires that the applicant show that the proposed invention has never appeared in the “prior art” in its exact form; prior art refers to all extant publications, patents, working inventions, and general knowledge as of the date of the claimed invention. In the United States, publication does not preclude a U.S. patent if the application is filed within one year of the publication date. Most other countries provide no such grace period.

To meet the element of nonobviousness, the applicant must demonstrate that the proposed invention required more skill and ingenuity than possessed by the average person working in the same field.

Infringement and Remedies

Obtaining a patent does not require the patent holder to practice, promote, or commercialize the invention. Once a patent is granted, enforcing exclusivity falls to the patent holder. In return for a payment, a patent holder may license his or her rights to others, either exclusively or nonexclusively. One who makes, uses, or sells a patented invention without the patent holder's permission, however, infringes that patent and generally gives rise to liability.

One judicially derived doctrine is particularly important as a defense against infringement. According to the doctrine of experimental use, pure research activities using a patented product, though technically infringements, are excused from legal liability. The applicability of this doctrine to molecular research and commercial development of biotechnological products is important, because lines between experimentation and commercialization often blur.

Biotechnology and Patents

Thomas Jefferson devised the U.S. patent system. Now over 200 years old, U.S. patent law has proved itself a durable incentive for the creation of millions of inventions. In contrast, biotechnology--both as a scientific art and business enterprise--is only 20 some years old. The recent interface of biotechnological products and patent law has raised other policy issues, in addition to the experimental use exception, which some commentators argue are unique to biotechnology.

For example, in Diamond v. Chakrabarty, the U.S. Supreme Court ruled for the first time that "anything under the sun that is made by man" is patentable subject matter, including human made

living microorganisms and nonhuman mammals. Other experts argue that the pace and nature of molecular biological research is unlike any before seen and that the patent process, which can involve periods of uncertainty as litigation sets precedents, may push biological research toward a period of increased secrecy until a clear path--or one perceived as more clear--matures.

Historically, however, Congress has singled out few industries for unique patent treatment. For example, patent law has been used to control innovation and development of atomic energy. In another instance, Congress legislated special treatment to the airline industry, allowing companies to pool patents to promote the then nascent industry's development without concern for anti-trust considerations.

Why the Controversy?

By the late 1960s, advances in biological and genetic technologies began to unlock the mysteries of human disease--largely from federally funded research. And in the 1980s, judicial and legislative policies expressly encouraged commercialization of biomedical research: From 1983 to 1988, the number of "biotechnology" applications filed grew at an annual rate of 20 percent--significantly higher than the 2.9 percent rate for all patent applications. Why the immediate and largely negative uproar among so many academic scientists, professional organizations, industry, and policymakers--both here and abroad--when NIH filed its application? In part, objections centered on the recognition that research in human molecular genetics increasingly will play a central role in the development of novel therapeutics, and that the commercial value from such pharmaceuticals will be significant.

Most scientists oppose the patenting of ESTs (table 1-3) on the belief that the amount of effort expended making the invention does not justify a scenario whereby an EST patent holder receives proprietary rights that may dominate the rights of a scientist who elucidates and characterizes the in

vivo function of the gene and gene product. Even if a full gene sequence is elucidated, as will increasingly become the norm, in the absence of further characterization of in vivo function, many researchers believe it unfair to allow patents on these results, since the intellectual effort involved generally is less than for functional characterization. Hence, if PTO disallows patents on these types of sequences, companies or other parties might opt to maintain their DNA sequences as trade secrets until their research reaches the stage at which they are comfortable that PTO will issue a patent; publishing such sequences (or making them widely available through public databases) prior to that point could jeopardize the opportunity of that company or individual--or even a competitor working on the same gene--to obtain a composition of matter patent and reap future rewards. In contrast, when patents are granted, the inventor must make a public disclosure about the subject matter. Moreover, patent law's purpose is to promote the progress of science and the useful arts, not to reward hard work per se with intellectual property rights while disallowing patents for that discovered through minimal labor. Just because it is easy to do does not mean it is not patentable.

Opponents of EST-like patents also worry about the prospects and potential consequences of allowing human DNA sequence patents en masse. If granted en masse, EST patents (or gene patents not fully characterized with respect to in vivo function) with broad claims to the entire gene and gene products could effectively place control for development and profit of thousands of genes into the hands of a single patentee--a notion many find objectionable, but with no foundation in patent law per se.

Who are the Stakeholders?

Once the NIH action was revealed, disagreement ensued among patent attorneys as to whether the law supported such an application. Within the Federal Government, the two principal agencies funding human genome research--NIH and DOE--sought to reconcile distinct opinions, and the two trade associations then representing the biotechnology industry staked different positions.

International opposition--represented by governments, professional organizations, and individuals--also was expressed. Likewise, academic researchers and professional societies in the United States voiced initial opposition.

The vast majority of stakeholders opined that regardless of the merits of the NIH application, patents were important to foster innovation in biotechnology. What is indisputable is that common to the disparate perspectives was the sentiment that public debate was welcomed. And underlying the wrangling, posturing, and positioning was the knowledge that potentially at stake were billions of dollars. Biotechnology companies raised over \$5 billion in 1992, and venture capital transactions involving biotechnology companies increased in value from \$217 million in 1991 to \$459 million in 1992.

ETHICAL CONSIDERATIONS

A central focus of the debate about the NIH patent application, particularly abroad and among policymakers, focused on broader ethical concerns related to patenting any human DNA sequence.

OTA found three moral questions lie at the heart of the controversy:

- Is it appropriate to patent human DNA sequences if they are viewed as part of humanity's common heritage and so should be in society's custody?
- Is patenting human DNA sequences compatible with respect for the dignity of human beings and human life?
- Will patents unfairly affect research and commercial efforts in developing nations?

Even with the withdrawal of NIH's patent application, moral arguments for and against intellectual property protection derived from human genetic material will continue to reflect evolving cultural and social concepts of common heritage and human dignity within the international scientific and lay communities. For example, current discussions related to the Human Genome Diversity Project (box 1-C) demonstrate that claims focused on common heritage and human dignity will persist

as moral dilemmas raised by ownership, management, and intellectual property protection of human biological material. Recently, an international controversy erupted about the ethics of patenting a cell line from an individual from an indigenous population in a developing country and led a Federal agency to withdraw the application.

A philosophical analysis of common heritage issues reveals that merely because human DNA sequences are found in nature as part of a common heritage might not be sufficient to prohibit intellectual property rights on moral grounds. For example, tangible property rights can be claimed to naturally occurring substances as minerals. Still, common heritage concerns might justify, on a moral basis, a system of property rights that includes an experimental use exception. There appears to be no moral imperative to reject patenting a specific human DNA sequence because it defines personal identity and so harms human dignity. A reductionist view that human DNA sequences alone are responsible for personal identity is false: Humans are not just walking DNA molecules. Moreover, the human genome shares significant similarities with animal, plant, and microbial genomes. Hence, since most human DNA sequences are not unique to the human species, human identity is not defined by these sequences. On the other hand, morally based objections against an application to patent an entire set of human genes can be demonstrated, as can moral arguments against patenting human DNA sequences for eugenic purposes. Finally, concerns that patents on human DNA sequences might exacerbate economic disparities among developed and lesser developed nations are largely based on concerns about common heritage, for which moral arguments are equivocal. Equity and justice are important moral considerations, but policymakers seemingly can approach these issues more effectively through means other than intellectual property protection.

IMPLICATIONS FOR RESEARCH AND DEVELOPMENT

Seeking patents on the results of biomedical research is not a new phenomenon; nor are such patents the sole province of industry. Since at least the turn of the century, universities considered the

income producing potential of patents on their research. Still, many researchers felt academic and government-funded science should be unadulterated by commercial considerations, on the belief that industrial commitments would foster secretiveness and impede the open exchange of information and research reagents; such notions were particularly strong in the biomedical sector.

One of the most vocal sectors opposed to the 1991 NIH patent filing was the academic-based researcher. Moreover, nonscientist opponents also expressed significant concern about the potential impact of the NIH move on individual scientists who might have spent years working toward identifying one of the genes encompassed by the application, only to be placed in a subservient intellectual property position by the U.S. Government, the likely funder of the investigator's work.

Nevertheless, a 1994 OTA survey of 253 randomly selected recipients of NIH grants awarded through study sections principally funding grants in human molecular biology found that although 91 percent of respondents felt "there is a trend toward the commercialization of academic research," as mentioned previously, a majority believed the NIH patent application would not affect their research. Moreover, the majority of researchers polled by OTA reported that commercialization of research has had no effect on several aspects of the academic research enterprise (table 1-4), although significant minorities felt that commercialization had a negative impact on the transfer of research materials or products and data sharing. Moreover, 43 percent of molecular biologists reported to OTA they were involved in collaborations with industry, generally because industry collaborations allowed the investigator to work with researchers and equipment not otherwise available.

With respect to commercial development of the Human Genome Project, OTA found increasing interest and investment by the private sector in what might be referred to as genome-related companies (table 1-5). As with commercialization in other U.S. industrial sectors, intellectual property protection will be important to the success of these ventures. But perhaps unique to these companies, as well as the broader commercial biotechnology sector, several of these ventures owe the

scientific basis for their existence to the commitment of Federal resources for biological research and technology transfer policies adopted in the 1980s.

FEDERAL TECHNOLOGY TRANSFER

Commercialization of federally funded research depends on transferring technology to industry, whose laboratories translate intellectual property into commercial products that benefit the economy and society. The filing of the NIH patent application was justified, in part, as an attempt by the Federal Government to ensure that the public investment's in biomedical research--in this case at a Federal laboratory--was optimized by seeking intellectual property protection that would be attractive to investment by potential industrial partners.

Such Federal-private sector partnerships, or academic-private partnerships, were made possible by a series of laws enacted in the 1980s. Today, an elaborate system of laws, regulations, and policies is in place to transfer the fruits of federally funded research--through grants or contracts at academic or research institutions, or at Federal laboratories--to industry (box 1-D). With respect to research conducted under the auspices of the Human Genome Project, NIH and DOE technology transfer policies are key.

From the Federal-private side, OTA found that NIH has made extensive use of its authority to enter into Cooperative Research and Development Agreements (CRADAs) with private firms. To date, most NIH research royalties come from inventions based on inventions and discoveries prior to 1986. Measuring returns from NIH CRADAs, at least by income, is difficult because many of the potentially lucrative NIH CRADAs involve therapeutic agents that have not completed the 8 to 10 years of clinical trials required by the Food and Drug Administration (FDA) before market approval. Viewed from the private side, however, participants at a 1994 OTA workshop who were drawn from

a broad spectrum of companies reported increasing frustration with the NIH technology transfer system of review, but especially potential pricing controversies.

Technology transfer at DOE centers on the national laboratories, and biomedical-related CRADAs reflect DOE funded research in drug development, diagnostics, therapeutics, and technologies for rapid DNA sequencing. Such applications are a minority of DOE CRADAs, however, as most of DOE's technology transfer focuses on its historical role in nuclear weapons and atomic energy. As the emphasis shifts to developing expertise in civilian technologies, however, biotechnological and genome innovation is likely to be increasingly important to DOE's technology transfer efforts.

Finally, the bulk of technology transfer in the life sciences takes place via the rich academic biomedical infrastructure that is unique to the United States. These institutions benefit from the level of support provided by Federal Government sponsorship, and in return have delivered the world's leader in biotechnological developments. The first 15 FDA-approved biotechnology products and vaccines were from U.S. enterprises. In fact, both the research base as well as the development of the companies. can trace their roots to academic research from the 1970s forward.

The Bayh-Dole Act of 1980 significantly boosted technology transfer at U.S. academic institutions. According to a survey of the Association of University Technology Managers, revenue to U.S. universities from technology licensing agreements grows by 25 percent annually, and in 1992, nearly 1,500 patents were issued to colleges and universities--four times the number issued in 1982. Today, technology transfer at most institutions is integral to to the university's structure and mission, but most do not generate income sufficient to self support their operations. As measured by income or patents, some institutions succeed more than others. But as a 1993 OTA survey of academic technology transfer managers revealed, the office and university view the primary goal as promoting

the public good by making federally. funded (and other) research results available for commercial development.

WHAT IS THE ROLE OF CONGRESS?

Since 1981, when OTA first evaluated the policy implications of genetic engineering in *Impacts of Applied Genetics: Micro-organisms, Plants and Animals*, through several reports on biotechnology or genetic research,¹ OTA consistently reported to Congress that intellectual property protection has played, and continues to play, a critical role in U.S. preeminence in commercial biotechnology. During the course of this assessment, OTA found no evidence to conclude otherwise, although OTA did find that the NIH patent application subtly altered many individuals' thinking about strategies for seeking patents on human DNA sequences.

OTA identified four policy issues related to the Human Genome Project and patenting DNA sequences. They are:

- the appropriateness of human DNA sequence patents,
- the adequacy of U.S. patent law to deal with biotechnological inventions,

¹U.S. Congress. Office of Technology Assessment, *Impacts of Applied Genetics: Micro-organisms, Plants, and Animals*, NTIS PB-206609 (Springfield, VA: National Technical Information Service, 1981); U.S. Congress, Office of Technology Assessment, [Commercial Biotechnology: An International Analysis](#), OTA-B-218 (Washington, DC: U.S. Government Printing Office, January 1984); U.S. Congress, Office of Technology Assessment, [Mapping Our Genes--Genome Projects: How Big, How Fast?](#), OTA-BA-373 (Washington, DC: U.S. Government Printing Office, April 1988); U.S. Congress, Office of Technology Assessment, [New Developments in Biotechnology: U.S. Investment in Biotechnology](#) (Washington, DC: U.S. Government Printing Office, July 1988); U.S. Congress, Office of Technology Assessment, [New Developments in Biotechnology: Patenting Life](#), OTA-BA-370 (Washington, DC: U.S. Government Printing Office, April 1989); U.S. Congress, Office of Technology Assessment, [Biotechnology in a Global Economy](#), OTA-BA-494 (Washington, DC: U.S. Government Printing Office, October 1991); U.S. Congress, Office of Technology Assessment, [Pharmaceutical R&D: Costs, Risks and Rewards](#), OTA-H-522 (Washington, DC: U.S. Government Printing Office, February 1993).

- the adequacy of mechanisms for the Federal government to analyze bioethical issues, and
- the adequacy of the Federal technology transfer system for human genome research.

Congress could play a role in each of these policy issues through its oversight or appropriation authorities, or both. With respect to the issues raised by DNA patents and the Human Genome Project, congressional attention could focus on NIH and DOE, the agencies responsible for funding the Human Genome Project, or the Department of Commerce, which oversees PTO and most technology transfer statutes.

Specific options for Congress to consider (table 1-X) build on the discussions earlier in this chapter and in chapters 3 through 6 of this report. Associated with each policy issue, discussed in turn in the following sections, are several options for congressional action that range from taking no specific steps to making major changes. Each option analyzes the potential consequences of its adoption, and also presents the views of differing stakeholders.

The order in which the options are presented does not imply their priority. Moreover, the options are not generally mutually exclusive: Adopting one does not necessarily disqualify others that pertain to the same or other issues, although changes in one area could have repercussions in others. A careful combination of options within and among the four policy issues could produce the most desirable effects.

ISSUE 1: Should patenting human DNA sequences be permitted?

Currently, the U.S. Patent and Trademark Office (PTO) grants composition of matter and process patents involving human DNA sequences--as long as an application meets the criteria of utility, nonobviousness, and novelty. In fact, PTO has issued patents involving human DNA sequences since at least 1980: OTA found that in the period 1980 through 1993, PTO issued X

human DNA sequence patents for a broad range of applications. Congress could consider, however, whether PTO may continue this practice.

Option 1.1 -- *No action.* In terms of patentable subject matter, U.S. patent law (35 U.S.C. 101) is the most inventor-friendly statute in the world. It is unique in that it makes no exceptions to patentability, which by contrast are often found in statutes of other countries (e.g., animal or plant varieties, or pharmaceuticals or foods). Congress could take no action if it determines that PTO's present application of patent law's requirements for patentability of human DNA sequences is adequate.

If Congress takes no action regarding patentable subject matter, PTO will continue to grant intellectual property protection for genome-derived inventions based on statutorily defined criteria. And, when appropriate, courts will resolve litigation brought by interested parties.

Maintaining the status quo with respect to patentable subject matter would satisfy U.S. biotechnology companies and the great majority of biotechnology patent attorneys, as well as most individuals involved in technology transfer or commercial development of human genome research. Moreover, if Congress takes no action, opposition from sectors outside biotechnology will not surface, which it surely would if Congress opted to amend the patent statute specifically for biomedical innovations. Proponents of taking no action believe that current law--with foundations in the Constitution--provides an appropriate system of checks and balances--i.e., PTO has flexibility to handle patents from genome research, but courts may assess and refine how PTO implements the law in light of new developments.

On the other hand, opponents of granting exclusive rights to human biological material (even if they meet the legal patentability requirements) and opponents of the Human Genome Project, would object to this option. A clear majority of academic researchers expressed to OTA the belief that PTO should not grant composition of matter patents for human gene sequences unless knowledge about the

protein and its role in vivo have been identified. Thus, some scientists believe congressional action is needed to define the scope of patentable genome-derived inventions, but as much to resolve the problem of uncertainty. In particular, academic researchers worry that if Congress takes no action, the problem of uncertainty extends, which in turn might increase secrecy and delay progress to map the human genome. Put another way, if a party is unsure about his or her ability to patent a DNA sequence, then the individual or company likely will opt to hold the DNA sequence secret instead of filing an early patent to establish priority and then making the DNA sequence available to other researchers through publicly available databases.

Option 1.2 -- *Enact a moratorium on the issuance of human DNA sequence patents.* As was proposed (but not adopted) for animal patents, Congress could direct PTO to suspend issuance of all human DNA sequence patents, or specify that PTO only allow process or use patents, while imposing a moratorium on composition of matter patents involving human DNA sequences. Congress could mandate the duration of the moratorium to allow further time for debate and discussion on the issues raised by this report.

Option 1.3 -- *Amend patent law to address patenting human DNA sequences.* Congress could determine that a moratorium is unnecessary and move immediately to address the policy issues raised by human DNA sequence patents. Such an action might signal Congress's intent that patenting human DNA is acceptable, but that boundaries must be drawn. That is, Congress could include any limitations or exceptions to subject matter patentability of human DNA sequences, deposit, or infringement. In fact, Congress adopted sector specific treatment for other industries--i.e., for atomic energy, the airline industry, and the semiconductor industry.

Historically, Congress has singled out a few industries for unique patent treatment. For example, patent law has been used to control innovation and development of atomic energy. In another instance, Congress legislated special treatment to the airline industry, allowing companies to

pool patents to promote the then nascent industry's development without concern for anti-trust considerations.

Predicting the positive or negative consequences of this option is impossible because any outcomes tie directly to what type of law Congress enacts, although the approach can be evaluated in general terms. Clearly, a downside to this option centers on the ability of any new law to address past perceived grievances and resolve pending concerns, yet predict and anticipate potential concerns without resorting to broad or vague language that might merely maintain the status quo or create new problems as courts attempt to interpret legislative intent. In particular, given the pace of research in human genetics, statutory language specifically directed to human DNA sequence patents could turn archaic in a matter of weeks or months, and certainly in a few years--i.e., predicting the course of genome research, on which any forward looking legislative language might be based, would prove tricky.

Additionally, success with sector-targeted legislation is mixed. Legislation directed toward the airline industry appears to have lowered transaction costs of licensing by allowing association members unlimited access to each other's patents, and it eliminated the uncertainties associated with litigation. The arrangement also did not slow the pace of technology development. On the other hand, legislation directed at the semiconductor industry was less clearly successful, in part because the industry and technology evolved beyond the capacity of the law's scope.

With respect to human DNA sequences, then, the airline industry legislation potentially serves as an attractive model. The structure of these two sectors differs markedly, however, which could make the airline industry approach inappropriate or undesirable--certainly for composition of matter patents. First, in contrast to biotechnology, the emerging airline industry involved a limited number of firms. Second, the potential inventions--i.e., airline parts--are well-defined and limited if compared to biotechnology and genome patents. The semiconductor industry model seems to offer less to human DNA sequences because the form of protection was copyright, not patents. Moreover,

semiconductors and biotechnology share the common feature of rapid technology development, which in turn contributed to making the law moot.

As with the previous option, most stakeholders would oppose this alternative. Those voices who oppose intellectual property protection for human DNA sequences per se would be less satisfied with this option than with an outright ban or moratorium, but likely would welcome the opportunity for legislative action on the broad issue of biotechnology patents.

Option 1.4 -- *Enact legislation explicitly providing for human DNA sequence patents.* As noted at the outset of this chapter, Congress has the authority to expand or restrict the kinds of inventions for which PTO may issue patents. Thus, Congress could provide explicit statutory protection for an area that has, as a practical policy and process, long existed; as OTA's analysis revealed, PTO has granted at least X human DNA sequence patents since 1980. In adopting this option, Congress would erase any doubt regarding whether human DNA sequences were intended as patentable subject matter.

If Congress were to limit this option to a declarative statement that human DNA sequences are patentable as composition of matter, there would be little practical impact; PTO and courts already have judged such is the case. On a pragmatic level, however, Congress could be inundated with requests for similar pronouncements if it proceeds with this option. Additionally, beyond a declarative statement, any attempts to define human DNA sequences or categorize classes of potential applications as permissible or prohibited runs afoul of the same difficulties discussed in option 1.3. Moreover, as a philosophical matter, questions would be raised as to why human DNA sequences require such legislation. And finally, this action appears to be unnecessary if Congress's sole intent is to permit human DNA sequence patents, yet could be interpreted by future court action as limiting the patentability of other kinds of inventions in the absence of explicit congressional approval.

It is difficult to envision any stakeholder class who would support this option. As mentioned previously, biotechnology companies, inventors, and their patent attorneys would be wary of opening the patent statute to affirm an existing state of affairs. Obviously, opponents of patents on human biological material would resist this option.

Option 1.5 -- *Enact a statute prohibiting human DNA sequence patents.* As with its authority to expressly permit certain patents, Congress could amend 35 U.S.C. 101 to explicitly prohibit composition of matter patents that involve human DNA sequences. Such action, which OTA presumes would not be retrospective, would bar all future patents involving human DNA sequences. Patents on protein products of important genes still could be allowed, which might serve the purpose of forcing applicants to fully characterize their DNA sequences and products before seeking intellectual property protection.

Yet, a prohibition on human DNA sequence patents could result in a redirection of investment in biomedical diagnostics and therapies to other commercial sectors. Without the incentive to recoup spending on research and development in exchange for market exclusivity, companies might abandon potentially promising DNA-based approaches and focus on traditional chemical strategies, which while useful and necessary are complementary to, not a replacement for, genetic medicine. Additionally, adopting this option is likely to foster secrecy; companies and researchers will hold their work as trade secrets until a protein product is developed. Hence, information that could be useful for improvements on existing commercial products or to further basic research would be unavailable, and progress derived from the research enterprise would lag.

In particular, this option would have a significant negative impact on applications for which a DNA sequence itself--and perhaps not even a full gene sequence--is the important product. For example, gene therapy--deliberately introducing genes into human cells to compensate for aberrant genes that cause genetic disease--would be affected, as well as other envisioned therapies using DNA itself as the therapeutic agent. Moreover, the entire field of molecular diagnostics would suffer.

Progress in human molecular medicine need not grind to a complete halt, however. As noted earlier, most genes are not uniquely human. Thus, the development of novel human diagnostics and therapies theoretically could move forward if Congress does not prohibit patents on nonhuman DNA sequences. The recent reports describing the identification of a colon cancer gene is a case in point; one group of investigators honed in on the human gene after it was armed with knowledge about similar bacterial DNA sequences. Whether this approach proves widely transferable, however, remains to be seen.

Nevertheless, if Congress chooses to pursue this option, only the small minority of individuals who oppose patenting human DNA sequences or other compositions of nature would be appeased.

Option 1.6 -- *Enact a statute prohibiting composition of matter patents on human DNA sequence patents, but allowing use patents.* Rather than completely ban patents that involve human DNA sequences, Congress could direct PTO to reject future composition of matter patents on human DNA sequences per se, while still permitting the patenting of processes or uses of human DNA sequence inventions. Such an approach would be similar to that adopted in many countries.

Again if Congress pursues this option, it would be the first legislative restriction on patentable subject matter without a national security interest at stake. Adopting this option would be viewed as weakening a patent statute that stands alone in inventor-friendliness, and could lead to reduced investment in research and development of genome-derived innovations. In turn, financial markets could be adversely affected and ultimately U.S. competitiveness in the pharmaceutical sector could decline. Though such an option would affect both U.S. and non-U.S. entities, U.S. companies, universities, scientists, and investors would bear by far the greatest burden: For human DNA sequence patents, nearly 80 percent of those issued to date in the United States were assigned to a U.S. company, the U.S. government, or a U.S. university or nonprofit research institution.

As with option 1.2, biotechnology companies and their patent attorneys (and other industrial sectors that rely on strong patent protection) would oppose congressional attempts to shift U.S. patent law in this direction. On the other hand, based on OTA's survey of a sample of U.S. molecular biologists, many scientists might support congressional efforts that explore this action because they view the patent system as a reward for what can be a difficult process of characterizing in vivo biological function of a particular human DNA sequence, even though the current U.S. system is intended to reward innovation, not the amount of work. International genome scientists likely would also welcome this option, since it reflects their existing frame of reference. Additionally, many international policymakers and patent attorneys might support, or remain neutral toward, this option--again, because it is a system with which they already have experience. Opponents of intellectual property protection for human biological material or other products of nature would be less satisfied with this option than an outright prohibition, but likely would prefer it to the status quo.

Option 1.7 -- *Direct PTO to consider the ethical considerations of patenting human DNA sequences and to clarify the Office's position through a public statement.* Until the 1980 Supreme Court's decision in Diamond v. Chakrabarty, PTO considered live organisms to be products of nature, and therefore unpatentable as composition of matter. PTO rejected applications directed to living organisms per se, but granted patent protection for many compositions containing living things, such as vaccines of attenuated viruses or food yeast compositions. In 1987, the Board of Patent Appeals and Interferences extended patentable subject matter to multicellular organisms, in this case a type of nonnaturally occurring oyster. This ruling and the knowledge that PTO was considering patents on vertebrate animals raised concerns about whether humans could be patented.

To forestall further debate on this issue, PTO, on its own initiative, announced in April 1987--even before it granted the Harvard mouse patent--that a "claim directed to or including within its scope a human being will not be considered to be patentable subject matter under 35 U.S.C. sec. 101." PTO declared that such an action would be unconstitutional, but its announcement made no reference

to a specific section of the Constitution (though most legal experts assumed the 13th Amendment was at issue). Thus, Congress--in its authorization, appropriation, or oversight role--could direct PTO to clarify its position on patenting human DNA sequences.

PTO likely would oppose this option, preferring to continue handling applications on a case-by-case basis. On the other hand, public interest groups likely would welcome this congressional action because it opens PTO's process, albeit on a limited basis. Even if these parties ultimately were dissatisfied with this particular statement, the general approach probably would be viewed with favor. Researchers, companies, and patent lawyers also might support this option for that reason: Clarifying issues and removing uncertainty generally benefits these stakeholders. In some respects, resolving uncertainty can be more important than resolving it in any particular way.

ISSUE 2: Is current U.S. patent law adequate to address biotechnology developments?

Rather than address the narrower question on patentability of human DNA sequences, Congress could opt to consider whether the current controversy surrounding the NIH EST application points to more generic questions about the ability of patent law to keep pace with the rapid pace of molecular biological research.

Option 2.1 -- No action. Congress could determine that current U.S. patent law as applied to biotechnological inventions is satisfactory and so take no action. In doing so, Congress would signal to companies, universities, researchers, and their patent lawyers that Congress itself does not intend to address the problem of uncertainty that some perceive currently exists. On the one hand, those concerned about infringement actions related to the use of patented materials in research or the impact of recent judicial decisionmaking on biotechnology process patents would oppose this option. Additionally, individuals concerned that biotechnological inventions raise special ethical considerations not confronted with traditional manufacturing or chemical patents would oppose congressional inaction. On the other hand, commercial sectors outside of biotechnology likely would prefer that

Congress take no action. Again as with several of the options reviewed for issue 1, a general reluctance to tinker with a 200+ year old statute exists among patent lawyers and companies.

Option 2.2 -- *Enact a statute defining and delimiting an experimental use exception.* Of particular interest to the biomedical research community is the judicially derived infringement exemption referred to as the experimental use exception. Because the line between basic research in biotechnology and research to develop a commercial product can blur, or quickly shift from one type to the next, Congress might opt to define by statute what constitute infringements for purposes of the experimental use exception to make clear to researchers when they should seek and pay for a license on a patented item. Regardless of the approach taken, however, those companies in the market of providing research tools might oppose such legislation since an exemption could diminish the market for these inventions.

Option 2.2.1 -- *Base such legislation on codification of judicially created experimental use exception.* Congress could enact a statute that codifies current judicial interpretation in this area. On one hand, such a statute could assuage those who fear infringement and litigation but have no means, or are reluctant, to enter into license after license to conduct their research. If such a statute truly clarifies what research is experimental and what is commercial, companies also might support this option. Still, as discussed for earlier options, the rapid pace of development in molecular biological research and the potential commercial value of much human genetic research would appear to make line drawing difficult. Moreover, Congress would need to decide if codifying an exemption should be limited to biotechnology inventions, or whether all sectors should be--or even could be--addressed.

Such a statute could be limited to an exemption that applies only to federally funded inventions of universities and nonprofit research institutions. This approach offers the advantage of avoiding what constitutes basic versus commercial research. On the other hand, it likely would be strongly opposed by the industry. Researchers at private enterprises argue that they consider academic,

federally funded colleagues to be equal rivals in the race to find scientifically interesting (and therefore, in molecular biology, commercially valuable) research results.

Option 2.2.1 -- *Base such legislation on the notion of compensated fair use.*

Congress could enact legislation that institutes some form of compensated fair use, which would define the conditions by which a patented invention may be used on which to base further inventions. For example, one scenario might be the identification of ESTs to obtain the genomic copy or use of a patented protein to design second generation products. Terms of compensation could be defined in the statute.

One advantage of this approach is that the current system is an all or nothing situation: either an experimental user is liable for infringement or the user goes scot free and the patent holder receives no reimbursement. This option aims to provide a step-wise progression of compensation. On the other hand, devising a system of compensation could prove problematic. Moreover, as the technological progress advances, this option--as with other options presented that attempt to address past harms, current issues, while projecting sufficiently to the future--might fall short of its intended goal of limiting the cloud of uncertainty that some believe results from the lack of a statutorily defined experimental use exception.

Option 2.2.3 -- *Direct NIH and DOE to develop a DNA sequence and patent database that promotes dissemination of DNA sequence information and also facilitates the exchange of patent rights in those sequences.* With respect to intellectual property protection related to human (and other) DNA sequences, the nature, implementation, and enforcement remedies might be less important than fostering the exchange sequences in a manner that both promotes exchange and preserves the opportunity to receive royalty income. Hence, Congress could direct NIH and DOE to develop a database that achieves these ends.

Currently, over 50 databases--public and private--collect and organize DNA sequence data and then make the data available electronically. Congress could direct NIH and DOE to examine the existing network of databases--as well as GenBank, a large federally administered database--so that the dissemination of the sequences themselves is optimized, but that the exchange of patent rights is also facilitated. For example, a separate patent holder field could be coupled to each record (the sequence), along with any fees or restrictions associated with use of the particular sequence. Some individuals placing sequences in the database could opt to waive their patent rights and could specify this in the record. Others might list a one time fee in the record and, ultimately, transactions even could be processed on-line via the database. Thus, both the goal of broad dissemination is met, while also preserving a patent holder's right to derive income from an invention. Moreover, such an approach could facilitate fee transactions, identify up front conditions for use of patented sequences, and potentially avoid the cost and uncertainty of litigation.

Most parties might welcome adoption of this option, although concerns about data integrity, cost of the database, and quality assurance would need to be addressed. Whether NIH or DOE would support or oppose this option would depend, in part, on whether the costs of developing such a database would be new or redirected funds. Moreover, Congress would need decide whether one, both, or neither agency oversees the implementation of this option.

Option 2.3 -- *Enact a statute to allow process patent protection on biotechnology methods even if the starting material is novel.* A 1985 court case, *In re Durden* upheld PTO's decision that a chemical process, otherwise obvious, is not patentable. Hence, Congress could enact a statute to overturn the *Durden* decision, and legislation has been introduced in the past three Congresses to do so.

Supporters of this option believe that unless Congress enacts a statute to overturn *Durden's* reach, biotechnology companies will find it nearly impossible to obtain process patents because recombinant DNA processes and automated DNA sequencing processes are obvious, though the

starting material might be novel. On the other hand, opponents--often from other industrial sectors--argue that any legislation will increase, not decrease, uncertainty and lead to additional patent infringement suits.

Option 2.4 -- *Enact a statute directing PTO to account for ethical implications of biotechnology patents.* Since the Supreme Court's 1980 ruling in Diamond v. Chakrabarty, which itself was the focus of ethical controversy, the question of whether PTO should base patent decisions at least in part on ethical considerations continues to resurface with a range of biotechnology patents, not just those for human DNA sequences. Congress could determine that PTO should consider ethical dimensions of biotechnological innovation and enact a statute directing them to do so. For example, Congress could instruct PTO to evaluate the notion of potential social utility when assessing the patentability of an application.

Directing PTO to consider ethical implications in its evaluations on biotechnology inventions would trouble many who believe that evaluating social utility is highly individualized and subjective, although decisions to issue patents also ultimately have a measure of subjectivity. Voices opposed to this option also ask why only biotechnological developments should be subjected to an additional standard. These individuals argue that if concerns about the moral ramifications of the Human Genome Project and biotechnology exist, then regulating the use or access to the discoveries should be explored, but that intellectual property protection of discoveries should be unimpeded. On the other hand, this option might satisfy those individuals who oppose patents on any biological innovation. It might also assuage those who seek to have society focus on the ramifications of biotechnology more broadly and so seek to increase dialogue in the context of patent law, which they view as a pivotal step for commercialization (and hence potentially wide distribution and dissemination.).

Option 2.5 -- *Enact a statute refining the definition of prior art with respect to DNA inventions or direct PTO to do so.* An invention may not be patented if it lacks novelty over the prior

art, and how PTO defines and applies this term is of particular concern to individuals and companies with patent applications involving DNA sequences. For example, many human gene sequences share sequence similarity with animal, plant, or microbial sequences, yet no general rule, or even PTO guidance, exists (e.g., "x" percent) for an individual to determine whether his or her sequence might be unpatentable if a similar sequence has been published or, of increasing concern has been placed in a publically available genome database. PTO evaluates each application and claim on a case-by-case basis, because a single base difference in a gene sequence might exert a significant effect on the gene product, but be meaningless another situation.

Still, scientists continually reiterate the importance to generating the human genome map of early disclosure and widespread dissemination of all human DNA sequences. If investigators all sequester their sequences from public databases in order to avoid prior art difficulties, progress in the Human Genome Project could grind to a halt. On the other hand, concern is expressed that if thousands of gene fragments (e.g., ESTs)--or even full gene sequences for which a putative in vivo function has not been assigned--are placed in public databases to speed genome mapping, future researchers who identify in vivo function could be precluded from a composition of matter patent because the DNA sequence had been dumped in a databank.

Thus, Congress could enact a statute clarifying the terms of prior art for the purposes of genome inventions (which in essence would apply to most biotechnology patents, due to the manner by which genetic information is coded and translated,) or Congress could direct PTO to issue a statement achieving the same goal, but offering the potential for flexibility as the science progresses. Clarifying the application of prior art to DNA patents could decrease the problem of uncertainty, although in any rapidly moving field, any statement soon could be obsolete.

Biotechnology companies and scientists might support congressional adoption of such and option, but other sectors probably would oppose it strongly. On the other hand, PTO would probably

oppose, on principle, any action that forces them to *a priori* state sector specific criteria for prior art considerations of DNA patents. Moreover, PTO would also object to restrictions that removes their flexibility in examining applications.

ISSUE 3: Are Federal mechanisms to examine ethical issues of human DNA patents adequate?

As mentioned previously, congressional interest in this assessment focused, in part, on the ethical considerations of patenting human DNA sequences. In the absence of an OTA study, how might such an analysis been conducted?

Option 3.1 -- No action. If Congress takes no action, the United States' current ad hoc approach to addressing issues with ethical dimensions will continue. As OTA has detailed elsewhere,² the governments of at least 27 nations on 6 continents have established national bioethics commission of some type or had legislation pending within the last year.

Opponents of this option believe that today's current fragmented approach has left the country lurching from bioethics crisis to crisis--e.g., the George Washington University embryo splitting experiments or the revelations of the Cold War human radiation experiments--without a body of experts for policymakers and the public to turn to for immediate advice. On the other hand, those who favor the status quo oppose establishing a new commission because of its annual cost (about \$2 million per year), because they believe sufficient activity takes place at academic centers, because they fear a new body will become mired in controversies surrounding abortion, as did the most recent effort 6 years ago; or a combination.

²U.S., Congress, Office of Technology Assessment, Biomedical Ethics in U.S. Public Policy, OTA-BBS-BP-105 (Washington, DC: U.S. Government Printing Office, June 1993).

Option 3.2 -- *Direct the Ethical, Legal, and Social Issues programs of NIH and DOE to increase funding of grants that examine the implications of increased commercialization and privatization of the Human Genome Project.* If Congress determines that existing mechanisms are adequate, but that insufficient Federal attention is being paid to the ethical, legal, and social aspects of commercializing genetic research, Congress could direct NIH and DOE to seek and award a greater number of grants with this focus. In doing so, Congress could direct that a greater proportion of such awards be made with existing funds, at the expense of other areas. Or, Congress could direct that more than the expected 5 percent NIH set aside and 3 percent DOE set aside from Human Genome Project appropriations be devoted to the ELSI programs--at the expense of the scientific and technical components--and that the increase funds be allocated to grants studying the implications of privatization and commercialization of the Project.

Option 3.3 -- *Enact legislation to create a national body to address the ethical, legal, and social implications of commercialization of the Human Genome Project, specifically, or to address this and other bioethical issues.* Congress could determine that a national body should examine the ethical, legal, and social issues of patenting human DNA sequences and enact legislation to create a commission to address only this topic--i.e., an ad hoc effort. Or, Congress could conclude that the rapid pace of molecular biological research--and biomedical and behavioral research developments in other fields--raises, or has the potential to raise, sufficient issues that a standing or term-limited commission is again warranted.

This option would be supported by those individuals who believe Congress should increase and facilitate increased dialogue on bioethical issues--for genome-related issues, broader issues, or both. Individuals who would prefer that Congress move directly to limit patents on genome products, or regulate their use, might oppose this option because they view it as stalling. And clearly, those who favor the status quo, as described in option 3.1, would oppose this option.

Option 3.4 -- *Direct appropriate Federal agencies to provide support within biomedical doctoral and postdoctoral training programs for educational efforts that foster interdisciplinary dialogue on the ethical, legal, and social implications of the Human Genome Project.* Each year, the Federal Government spends nearly \$X million in doctoral and postdoctoral training. Congress could decide that encouraging newly trained scientists to explore the ethical, legal, and social implications of the Human Genome Project during the course of their scientific research is desirable. Thus, Congress could direct Federal agencies to restructure existing programs and require that recipients of Federal training funds devote a portion of these resources to such an effort.

Institutions, departments, or researchers currently receiving doctoral or postdoctoral training funds likely would object to having conditions placed on these monies--especially since the past X fiscal years have seen an X decline funds for training purposes. On the other hand

ISSUE 4: Is the Federal technology transfer system adequate for human genome research?

Option 4.1 -- *No action.* When Congress passed the Stevenson-Wydler Technology Innovation Act of 1980 (Public Law 96-480), the process of transferring technology began to take its current form. For life sciences research conducted in Federal laboratories, technology transfer, as measured by the rate of Cooperative Research and Development Agreement (CRADA) formation, proceeded at a faster rate at NIH in the 1980s, than at DOE--the two agencies responsible for the Human Genome Project. If Congress takes no action, CRADA formation at NIH and DOE will proceed, though whether at the current rate is less clear. (OTA did not analyze CRADAs at other agencies, but an ongoing assessment is examining technology transfer and the Federal laboratories more broadly).

If Congress takes no action, those individuals concerned about what they view as corporate exploitation of federally funded research in the biological sciences and the public's return on its investment likely would object to the status quo. Additionally, OTA's perception was that an

increasing number of biotechnology companies have begun to complain about the slowness and ineffectiveness of Federal technology transfer at NIH or DOE. Moreover, recent controversies related to drug pricing, sponsored research agreements, and conflict of interest issues reportedly have made companies increasingly reluctant to enter into CRADAs. Even if Congress takes no action at this point, it might opt to monitor CRADAs and technology transfer through its oversight function.

Option 4.2 -- *Direct the NIH Director to consolidate the collective/agency-wide review process for CRADAs.* OTA found a general sentiment that companies viewed the NIH CRADA review process as sometimes arbitrarily and unnecessarily bureaucratic--particularly when the elements of the model CRADA agreement are apparently adhered to; the number of meetings required for approval of life science CRADAs at NIH can cause companies seeking potential collaborative arrangements to withdraw from the process. If Congress views CRADAs as a key vehicle for private parties to commercialize biomedical research conducted at Federal laboratories, Congress could order the NIH Director to review the current mechanism with an eye toward consolidating the number of meetings and reviews necessary for CRADA approval at NIH's institutes and centers.

Streamlining the meetings held by the NIH Patent Policy Board and its subcommittees, including the CRADA subcommittee at the Office of Technology Transfer (OTT) and at the individual institutes, would expedite the process of technology transfer. Numerous sources within NIH and companies with CRADA experience at NIH have reported to OTA what they perceived as an inordinate amount of duplicative review required for CRADA approval, which they claim serves no useful purpose. Pursuing this option might enhance the ability of NIH to transfer research results to companies in the long run, regardless of uncertainties related to drug pricing and conflict of interest.

Reducing the level of scrutiny would be opposed to individuals concerned about the existing lack of NIH expertise to address issues related to drug pricing.³ On the other hand, congressional action to encourage consolidation of the CRADA review process would be viewed favorably by companies interested in collaborating with NIH in the life sciences.

Option 4.3 -- *Address the issue of public equity and access to inventions derived from federally funded research.* One underlying premise of Federal technology transfer is the benefit the public derives because potentially valuable research will be developed faster and more efficiently. Prior to 1980, companies wishing to exploit government patents faced 26 different sets of agency regulations, and although NIH had institutional patent agreements with 65 universities, which allowed them the first option to patent results of NIH-supported research, many Federal agencies still retained title to patents generated by their research programs. Data indicated, however, that this practice discouraged the transfer of the patented technology to the marketplace: In 1963, the Federal government held 14,000 unexpired patents, but could license only 1,200 of them; in 1975, it owned about twice as many, but again was able to license only 1,200.

Increasingly, however, concern is expressed by some about optimizing the Federal technology transfer system to maximize the benefit on the public's research investment. At issue with these individuals is the matter of equity: Citizens, whose tax payments fund Federal research conducted at Federal laboratories and fund federally-sponsored research conducted by private researchers and academic institutions, should receive maximum benefit from their payments.

Maximizing benefit to achieve equity can be viewed from several perspectives, however. As just mentioned, one benefit is increased availability to products that had previously gone undeveloped.

³U.S. Congress, Office of Technology Assessment, Pharmaceutical R&D: Costs, Risks and Rewards, OTA-H-522 (Washington, DC: U.S. Government Printing Office, February 1993).

Another could be affordability of the final product.⁴ Still another form could involve decreasing the taxpayer contribution to biomedical research, but supplementing funding with income from other sources, such as licenses from products derived from Federal funding.

Patenting arguably threatens the concept of taxpayer equity because individuals pay for the research leading to the discovery and--if the results are patented and licensed to a company to develop the discovery--pay again when they purchase the product because the product's price includes the licensing fee paid to the Government. Some argue that the Government should not patent its inventions at all, so that the public may have "free" access to inventions. Still, as was discovered prior to enactment of enhanced technology transfer laws, free access results in no access. The public suffers because the discoveries are not translated into products. Still, one approach to equity could be for Congress to address the manner in which federally owned patents are licensed.

Congress could consider two options for licensing patents held by the Federal Government if it believes the issue of equity should be addressed for Federal patents; these options are not intended to apply to patents owned by universities, institutions, or individuals that are the results of federally sponsored research. Currently, agency procedures and policies and market forces set licensing fees and terms for government inventions. On the one hand, the market might not adequately represent the equity interests of the public, setting Federal licensing returns too low. On the other hand, competitive market forces could keep prices on consumer products lower, resulting in direct, day-to-day benefit to the consumer of that product.

Option 4.3.1 --Enact legislation requiring compulsory licensing of all Federal patents. Such an approach would require an agency to license its discoveries so they are available for commercial development; licensing could be on an exclusive or nonexclusive basis.

⁴Examining issues related to price controls and CRADAs was beyond the scope of this report, but is the focus of an OTA report expected in summer 1994.

On the one hand some government inventions might not have commercial potential or broad enough market demand. Thus, requiring licenses be granted does not ensure that the public's interest in benefiting from discoveries will be met and could result in funds being wasted pursuing licenses--i.e., royalty income might increase, but the expansion might not offset the increased costs incurred to find licensing partners. On the other hand, agencies might save funds through altered, and perhaps more judicious, decisionmaking in pursuing patents. Another possible consequence might be that agencies opt to conduct more applied research, so that any potentially patentable research results would be more likely to meet a commercial demand.

Opponents of this option argue that compulsory licensing ultimately removes, not enhances, incentives for commercial development. Moreover, should compulsory licensing move research at Federal laboratories toward applied research, most scientists at these facilities would oppose a compulsory licensing scheme. On the other hand, those that perceive increased Federal technology transfer (and hence product availability) and licensing income would result from this option would argue it maximizes the public's investment in an era of diminishing resources.

Option 4.3.2 -- *Require a minimum license price, set as a percentage of the Federal investment in the discovery.* To ensure that each discovery has a minimum financial return when a Federal patent is licensed, Congress could require a minimum percentage based on the Federal investment. Recouping investment costs might be funneled back into further research, and might avoid to reduce research budgets if Federal funding for biomedical research constricts.

On the other hand, setting a minimum price for licensing Federal discoveries might remove market forces as the factor driving licensing fees and royalties. Companies might opt to ignore commercializing Federal patents for which they might otherwise have risked investment if the minimum price is high because the research was expensive. Alternatively, if a license included a minimum price commercial interests were willing to pay despite the risk, the increased price could be passed to the consumer--i.e., achieving access, but defeating the goal of equity. A minimum price for

licensing Federal discoveries could arbitrarily inflate the price of the licensing structure to a point where companies are no longer interested in pursuing a license on a Federal patent. Alternatively, if a license included a minimum price commercial interests were willing to pay, the purchase price of the product may be inflated (to include the cost of obtaining the license) defeating the goal of equity.

PROSPECTS FOR THE FUTURE

The past decade's confluence of biotechnology and patents has produced a surge of litigation. Such litigation is not surprising, however, given the web of partially overlapping patent claims, the potential high-value products, the problem of prior publication, and the fact that many researchers and companies are interested in the same products. How PTO and the courts interpret biotechnology patent claims, including genome claims, will continue to be an issue in the next few years.

Although NIH has withdrawn its EST patent application, the problem of uncertainty remains. Commercial ventures have proceeded with similar applications, and discussions surrounding the scope and nature of the claims sought by these applications will be, as with any other patent action, confidential matters between the applicant and PTO. Unless a patent issues from one of these applications, or until an applicant files a court action, any indication of the direction of resolution stays secret. In contrast, the NIH application involved taxpayer financing and so resulted in widespread and ongoing public discourse.

The NIH patent application highlights the tension that exists between the law and science--a tension that might continue and spread as genetics research progresses. Overall, all stakeholders face future uncertainty over whether they can secure clear title to rights on work they perform to characterize a particular gene. Despite this potentially adverse impact, however, OTA found a majority of academic molecular researchers surveyed believed that even if the NIH applications had been granted, their research would be unaffected--though a majority speculated that the research of their colleagues would be adversely affected. Patent lawyers, on behalf of their clients will continue to

seek the broadest protection possible for genome-derived patents; to do otherwise would breach their duties, but perpetuates the tension between the science and law. And, although the biotechnology industry--probably the stakeholder most affected by problems of uncertainty--expressed vocal opposition or consternation when NIH initially filed its applications, the passage of time has muted concerns about the uncertain future. By early 1994, OTA found biotechnology companies seemed willing to accept uncertainty until PTO or court decisions issue and unwilling to consider changes to U.S. patent law.

It is impossible to state categorically whether any single, pending human DNA sequence patent application of the NIH type will stifle or enhance research and development of new diagnostics and therapies. Patents on ESTs, an early stage development compared to fully sequencing and characterizing in vivo function, might reduce the reward--and hence, incentive--for the developments and improvements that bring biotechnological products to consumers. On the other hand, allowing patents on ESTs or complete gene sequences of unidentified in vivo function fosters dissemination, could accelerate commercialization of valuable genome-derived products, and could facilitate the construction of a human genome map. From a policy perspective, striking a balance that optimizes such trade-offs is key. One thing is clear, private sector investment and interest in the Human Genome Project is increasing, as its Federal funders intended. Hence, in the near term, evaluating the public-private partnership, as well as the international nature, of human genome research could prove important.

Two additional issues that might face Congress in the future are not specific to human genome research, but considering human genome research as a snapshot of a significantly larger picture does illuminate the difficulties. First, several issues relate to the initial intent of the Federal technology transfer system, the changing climate of Federal spending, and current and future expectations from technology transfer. Ongoing controversies center on the pricing of products based on federally funded R&D; conflict of interest, and recouping the public investment in Federal R&D.

Ultimately, Congress and the executive branch will struggle to address these issues in the broader context of Federal technology transfer, intellectual property, R&D and economic policy. Additionally, international considerations (e.g., patent harmonization and research collaboration) will increasingly be important to evaluating these issues, in particular for a global scientific endeavor like the Human Genome Project. Nevertheless, focusing on one sector--even if cast as broadly as biomedical research--could be at the expense of other sectors and result in an more inefficient and costly process.

Box 1A--Terminology

Many terms of art have been used to describe the current debate on patenting human DNA sequences. For the purposes of this report, OTA uses several terms in the following manner.

Human DNA sequences and *human genome* sequences (and *human DNA* patents or *human genome* patents) are the broadest terms used by OTA. They refer to an ex vivo length of an ordered sequence of nucleotides, generically; whether an in vivo function or association is known, putatively suggested, or unknown is not implied by the use of these terms.

In contrast, *gene* sequences (and *gene* patents) is used to refer to those DNA fragments for which a specific biological product or in vivo function has been demonstrated and associated with the ordered sequence of nucleotide base pairs. *Expressed sequence tag* (EST) refers to the type of DNA piece for which NIH seeks intellectual property protection. Namely, a known human DNA sequence presumed to be a partial gene sequence by virtue of the method used to produce it. In this report, OTA resists using the term *cDNA* sequences (or *cDNA* patents) to avoid the necessity of qualifying whether cDNA refers to a full length (or nearly full length) DNA sequence of assigned (i.e., a gene sequence) or unassigned function, or a partial DNA sequence presumed to be from a gene (i.e., an EST).⁵

SOURCE: Office of Technology Assessment, 1994.

⁵The term “cDNA” is used if directly quoted from a source, with OTA translating to the appropriate term under this definition scheme, if discerning such an interpretation from the source is possible.

Box 1-B--The National Institutes of Health's DNA Patent Application

Until summer 1991, as advances in human genetic research incrementally progressed, researchers, universities, and biotechnology companies filed and received a range of human DNA sequence patents for diagnostic, therapeutic, or research purposes. In June 1991, however, many felt this orderly process, or at least one perceived as orderly, was altered when NIH sought intellectual property protection on more than 6,000 short sequences of human DNA (ESTs) that, by the nature of their isolation method, coded for putative human genes and therefore human proteins, but were themselves incomplete gene sequences.

International and domestic reaction to NIH's maneuver was swift and primarily negative. Though the DNA sequences encompassed by the NIH application were acknowledged to be fragments of genes, NIH sought protection to the entire putative gene and its protein product. Never before had such broad-based and far-reaching claims for so many human-derived products been sought by a single applicant, irrespective of the fact--though not insignificant--that the sequences disclosed were not for complete genes nor individually associated with specific biological functions. Moreover, because the U.S. Government filed the application, a process usually conducted in secret was debated and scrutinized largely in public--a situation acknowledged by both opponents and proponents as desirable, especially once similar actions by the private sector came to light.

In fall 1992, NIH announced that PTO had rejected its initial application--as it does for most first applications. PTO ruled the NIH application lacked novelty, utility, and was obvious. NIH responded to PTO's rejection in February 1993, modifying the claims, but PTO again rejected the application. A year later, in February 1994, facing a deadline to further appeal PTO's rejection, NIH withdrew the application. Nevertheless, its legacy challenged conventional thinking about strategies for seeking patents on human DNA sequences, spotlighted the role of Federal technology transfer in biotechnological innovation, and underscored the perception that molecular medicine will play a pivotal role in ameliorating disease.

SOURCE: Office of Technology Assessment, 1994, based on R.G. Adler, "Genome Research: Fulfilling the Public's Expectations for Knowledge and Commercialization," Science 252: 1651-1656, 1991; C. Anderson, "U.S. Patent Application Stirs Up Gene Hunters," Nature 353: 485-486, 1991; R.M. Cook-Deegan, R.M., The Gene Wars: Science, Politics, and the Human Genome (New York, NY: W. Norton, 1994); B. Healy, "On Gene Patenting," New England Journal of Medicine 327: 664-668, 1992; T.D. Riley, "Patents on Random Complementary DNA Fragments," Science 257: 915-918, 1992; Office of Science and Technology Policy, Federal Coordinating Council for Science, Engineering, and Technology, Committee on Life Sciences and Health, Genome Patent Working Group, Federally Funded Genome Research: Science and Technology Transfer Issues--Proceedings of a Public Meeting, May 21, 1992.

Box 1-C--The Human Genome Diversity Project

While the Human Genome Project seeks to map and sequence a Caucasian “reference” genome, the Human Genome Diversity Project proposes to explore human genetic variation, both normal variation and variation responsible for inherited disease. Project supporters seek to examine the DNA of unrelated individuals from 400 to 500 populations of historical interest around the globe. By revealing as much as possible about the current state of genetic diversity among humans, the proposed project aims to answer: How has human variation evolved? To what extent can variation in disease risk be explained by human genetic diversity? How are human societies structured? Where did modern humans come from?

Several technical aspects of the proposed Human Genome Diversity Project remain to be settled. Moreover, the proposed project also must resolve several ethical, cultural, and social issues. In particular, since genetic differences are the proposed project’s focus, concerns are raised about information being used to support notions of superiority of one group over another and reinforce conventional views of race and ethnicity. Concerns are also raised about potential conflicts between U.S. regulations governing human subjects research and the practices, values, or beliefs in other societies. Finally, the Human Genome Diversity Project raises questions related to intellectual property rights for individuals, researchers, and nations--a particular concern since many of the populations proposed for sampling live in developing nations that have already expressed concerns about international justice and resource allocation issues surrounding DNA patents.

SOURCE: Office of Technology Assessment, 1994.

Box 1-D--Federal Technology Transfer Laws

Bayh-Dole Act of 1980 (Public Law 96-517)--Bayh-Dole became the first in the series of laws enacted by Congress to enhance the flow of federally funded science and technology to the private sector. Bayh-Dole was intended to provide a set of Federal rules governing patent law that could then be used to enhance technology transfer from federally funded research to industry. Bayh-Dole excluded, however, research at Federal contract laboratories until the act was amended in 1984. The 1984 amendments also designated the Department of Commerce as the lead agency for implementing the law and for overseeing Federal technology transfer.

The Stevenson-Wydler Technology Transfer Act of 1980 (Public Law 96-480)--Enacted the same year as Bayh-Dole, Stevenson-Wydler codified several Federal policies to encourage Federal agencies to transfer technology developed at Federal facilities. Under Stevenson-Wydler, Federal agencies shall devote 0.5 percent of their research budgets to the support of technology transfer at legislatively mandated Offices of Research and Technology Applications.

The Federal Technology Transfer Act of 1986 (FTTA Public Law 99-514)--Congress passed FTFA when it became apparent that despite Bayh-Dole and Stevenson-Wydler, relatively few technologies were being transferred. FTFA alters the emphasis from one of permitting technology transfer to requiring Federal technology transfer, and provides the authority for Federal agencies to negotiate Cooperative Research and Development Agreements (CRADAs) with nongovernment parties. FTFA moved negotiating from agency headquarters, in some circumstances, and authorized award programs as incentives for Federal employees who invented products with commercial worth.

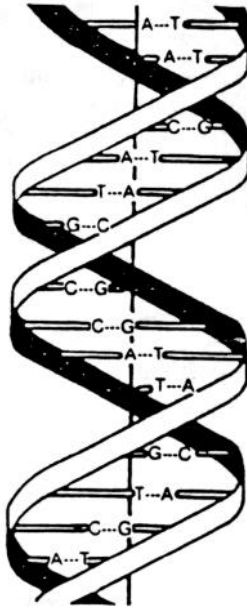
The Omnibus Trade and Competitiveness Act of 1988 (OTCA Public Law 100-418)--The focus of this law was to enhance U.S. economic competitiveness relative to other nations. OTCA established regional centers through a technology extension program, and strengthen the certain administrative capabilities of the newly named National Institute of Standards and Technology (former

National Bureau of Standards) and the National Technical Information Service, again with the goal of addressing U.S. competitiveness.

The National Competitiveness and Technology Transfer Act of 1989 (NCTTA; Public Law 101-189)--Congress enacted NCTTA in a further attempt to open research performed at the national laboratories to industry. NCTTA authorized DOE's contractor laboratories to enter into CRADAS as on equal footing with Federal facilities like NIH.

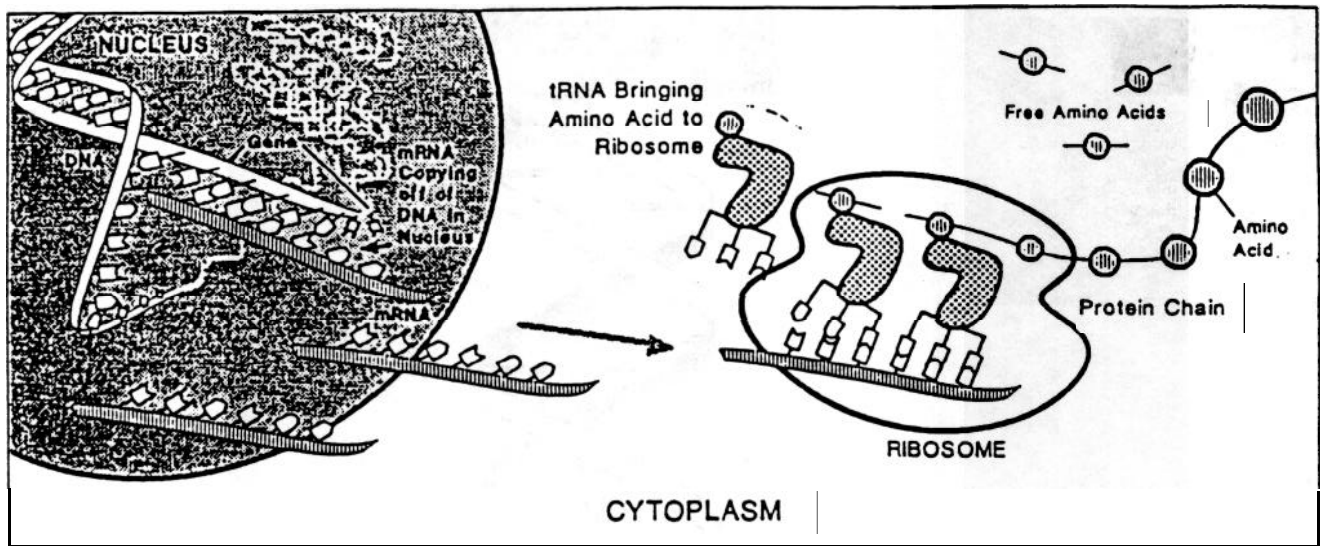
SOURCE: Office of Technology Assessment, 1994.

Figure 1-1--Structure of DNA



SOURCE: Office of Technology Assessment, 1994.

Figure 1-2--Gene Expression



In the first step of gene expression, messenger RNA is transcribed from DNA. In higher organisms, this process takes place in the nucleus of a cell. In response to certain signals, sequences of DNA adjacent to, or sometimes within, genes control the transcription to mRNA. The second major step in gene expression involves translating the mRNA sequence into a protein product. mRNAs are known as such because they carry messages specific to each of the 20 different amino acids that generally make up proteins. Once synthesized, mRNAs leave the nucleus of the cell and migrate to another cellular compartment the cytoplasm, where their messages are translated into the chains of amino acids that make up proteins. A particular sequence of three bases in the mRNA codes for an amino acid, and the main component of the translation machinery is the ribosome--a structure composed of proteins and another class of RNAs, ribosomal RNAs. The ribosome reads the genetic triplet code of the mRNA, while a third RNA molecule, transfer RNA (tRNA) effects protein synthesis by bringing specific amino acids to the ribosome for attachment to the growing amino acid chain until the full protein is synthesized and released from the ribosome.

SOURCE: Office of Technology Assessment, 1994.

Table 1-1--The Science and Politics of Patenting DNA

1865	Discovery of laws of heredity.
1910	Location of genes on chromosomes.
1917	The word “Biotechnologie” is coined in German.
1938	The term “molecular biology” first used.
1944	DNA identified as the genetic material.
1945	First patent for isolating nucleic acid issued.
1948	The concept of “molecular medicine and molecular disease” first noted.
1953	Watson and Crick elucidate Discovery of the structure of DNA.
1973	In vitro construction of recombinant DNA molecule.
1975	The Asilomar Conference urges adoption of guidelines for recombinant DNA research, setting a precedent of scrutiny and caution in molecular biological research.
1980	Stanford University is awarded a patent on the basic technique underlying recombinant DNA.
1985	Scientists debate the feasibility and merits of mapping and sequencing the human genome.
1987	Congress appropriates fiscal year 1998 funding for the Human Genome Project
1991	National Institutes of Health files its first patent applications based on a catalog of partial human gene sequences.
1994	National Institutes of Health withdraws EST patent application.

SOURCE: Office of Technology Assessment, 1994, based on T.D. Brock, The Emergence of Bacterial Genetics (Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press, 1990); R Bud, “100 Years of Biotechnology: Events and Publications That Moulded the Industry’s Place in Society,” Bio/Technology 11: S14-S15 1993; R.M. Cook-Deegan, The Gene Wars: Science, Politics, and the Human Genome (New York, NY: W.W. Norton, in press); and A.E. Tanenholtz, “Genetic Engineering--Technological Trends From the Perspective of a U.S. PTO Examiner, Fourth Annual Biotechnology Law Symposium (Clifton, NJ: Prentice Hall Law & Business, 1988).

Table 1-2 not included.

Table 1-3--Researchers' Reasons for Disapproval of NIH Patent Application

“Do you disapprove of NIH’s filing for EST patents because you believe...	Percent Yes
EST patents would inhibit data sharing among researchers.”	80
patenting a gene with such minimal effect will discourage the greater efforts needed to characterize biological function and subsequent diagnostic and therapeutic use.”	79
it is not ethical for any group to patent human DNA.”	41
it would inhibit private investment in genome research.”	36
it is not appropriate for the government to seek financial return on taxpayer supported research.”	28

SOURCE: Office of Technology Assessment, 1994, based on a 1994 OTA survey of 253 molecular biologists receiving grant funds from the National Institutes of Health.

Table 4--Researchers' Assessment of Commercialization's Effect on Academic Research

	Positive Effect	No Effect	Negative Effect	Not sure^a
Your collaboration with industry within the U.S.	38 Percent	57	4	2
International research collaboration	20	68	8	4
Goals and priorities	15	70	14	1
Transfer of research materials or protocols	12	58	29	1
Data sharing	8	59	32	2
Conflicts of interest	8	68	19	5
Publication	8	73	19	1

^aPercentages may not add to 100 due to rounding.

SOURCE: Office of Technology Assessment, 1994.

Table 1-5--U.S. Companies Involved in Sequencing and Mapping the Human Genome

Company	Research Plan	Capitalization as of 12/93
Collaborative Research	Use of semi-automated mapping, positional cloning, and semi-automated multiplex sequencing to locate genes for therapeutic development	\$3.5 million (NASDAQ)
Darwin Molecular	Focus on rapid DNA sequencing to screen and amplify potential pharmaceuticals	Estimates of \$50 million (VC)
Human Genome Sciences	Selling or licensing genetic information from the Institute for Genomic Research to pharmaceutical companies (NASDAQ)	\$259 million
Incyte Pharmaceuticals	High speed sequencing to find genes and corresponding proteins	\$56 million (American Stock Exchange)
Mercator Genetics	Use of positional cloning or "reverse genetics" to develop common disease therapeutics	unknown (V.C.)
Millenium Pharmaceuticals	Use of genome mismatch scanning to isolate genes related to diseases and target them for drug development	Estimates of \$8.5 million (VC)
Myriad Genetics	Focus on development of diagnostic tests for disease genes	Estimates of \$12.3 million (VC; Eli Lilly)
Sequana Therapeutics	Use of positional cloning to find and isolate genes for diagnostic and therapeutic purposes.	Estimates of \$5 million (VC)

VC = venture capital funding

SOURCE: Office of Technology Assessment, 1994, based on R.M. Cook-Deegan, "Survey of Genome Science Corporations," contractor document prepared for the Office of Technology Assessment, U.S. Congress, January 1994; and L. Fisher, "The Investment Allure of Biotechnology Stocks," New York Times, Dec. 3, 1993.

Table 1-6--Summary of Policy Issues and Options for Congress

ISSUE 1: Should patenting human DNA sequences be permitted?

Option 1.1--No action.

Option 1.2--Enact a moratorium on the issuance of human DNA sequence patents.

Option 1.3--Enact a statute amending patent law to address patenting human DNA sequences.

Option 1.4--Enact a statute explicitly providing for human DNA sequence patents.

Option 1.5--Enact a statute prohibiting human DNA sequence patents.

Option 1.6--Enact a statute prohibiting composition of matter patents on human DNA sequence patents, but allowing use patents.

ISSUE 2: Is current U.S. patent law adequate to address biotechnology developments?

Option 2.1--No action.

Option 2.2.1--Enact a statute defining and delimiting an experimental use exception based on the judicially created experimental use exception.

Option 2.2.2--Enact a statute defining and delimiting an experimental use exception based on the notion of compensated fair use.

Option 2.2.3--Direct NIH and DOE to develop a dna sequence and patent database that promotes dissemination of sequence information and also facilitates the exchange of patent rights in those sequences.

Option 2.3--Enact a statute to allow process patent protection on biotechnology methods even if the starting material is obvious.

Option 2.4--Enact a statute directing PTO to account for ethical implications of biotechnology patents.

Option 2.5--Enact a statute refining the definition of prior art with respect to DNA inventions or direct PTO to do so.

ISSUE 3: Are Federal mechanisms to examine ethical issues of human DNA patents adequate?

Option 3.1--No action.

Option 3.2--Direct the Ethical, Legal, and Social Issues programs of NIH and DOE to increase funding of grants that examine the implications of increased commercialization and privatization of the Human Genome Project.

Option 3.3--Enact legislation to create a national body to address the ethical, legal and social implications of commercialization of the Human Genome Project, specifically, or to address this and other bioethical issues.

Option 3.4--Direct appropriate Federal agencies to provide support within biomedical doctoral and postdoctoral training programs for educational efforts that foster interdisciplinary dialogue on the ethical, legal, and social implications of the Human Genome Project.

ISSUE 4: Is the Federal technology transfer system adequate for human genome research?

Option 3.1--No action.

Option 3.2--Direct the NIH Director to consolidate the collective/agency-wide review process for CRADAs.

Option 3.3.1--Enact legislation requiring compulsory licensing of all Federal patents.

Option 3.3.2--Enact legislation requiring a minimum license price, set as a percentage of the Federal investment in the discovery.

CHAPTER 2

INTRODUCTION

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"Genome projects raise no new questions of patent or copyright law."

Office of Technology Assessment
Mapping Our Genes, 1988 (OTA 1988a)

We were wrong. Beginning in summer 1991 and through the next several months, the National Institutes of Health (NIH) applied for patents on thousands of human DNA sequences of uncharacterized biological function (box 2-A), but believed to represent approximately 5 percent of all human genes. Hard on the heels of this action, other countries and at least one company and one university made similar filings (Owen, 1992; Anderson, 1993; OTA 1993). Commercialization of biomedical research, always a reality, entered a new realm (box 2-B).

WHY THE CONTROVERSY?

Seeking patents on the results of biomedical research, however, is not a new phenomenon (Kevles, 1993). Still, recent advances in biological and genetic technologies--coupled with judicial and legislative policies that enhanced the commercial potential of the fruits of biological research--have led to an avalanche of patent applications. From 1983 to 1988, the number of "biotechnology" applications filed grew at an annual rate of 20 percent--significantly higher than the 2.9 percent rate for all patent applications (OTA, 1991b). Why, then, the consternation about the NIH filings among so many academic scientists, professional organizations, industry, and policymakers--both here and abroad (OSTP, 1992)? Answers to this complex question lay, in part, in the recognition that:

- new developments in biotechnology hold great promise for improving human health;
- many biotechnology products already marketed, and many awaiting approval, perform functions not achieved by other drugs--i.e., they represent entirely new classes of therapeutic agents;
- research in human molecular genetics increasingly will play a central role in the development of novel therapeutics; and
- the potential commercial value from such pharmaceuticals can be significant (OTA, 1988a; OTA, 1993a).

Molecular biological research and the industrial sector it spawned, biotechnology, are established sources of innovation in pharmaceutical research and development, contributing both production technologies and research tools. Biotechnology is likely to be the principal scientific driving force for the discovery of new drugs as we enter the 21st century, and the impact of biotechnology on the discovery of new therapeutic entities is difficult to underestimate (OTA, 1991b).

The Moore Case

Even before scientists embarked on the Human Genome Project (box 2-C), scientists, industry, and investors recognized the potential of products derived from human biological material and the importance of intellectual property rights to such products. By the late 1970s, this potential had penetrated the public's consciousness.

In 1976, physicians informed John Moore he had a rare form of cancer, hairy cell leukemia, which affects about 250 Americans each year. Doctors performed the recommended treatment, removal of the spleen, at the University of California, Los Angeles Medical Center. As a patient, Moore signed a standard surgical consent form providing for the postoperative disposition of the diseased spleen, which had enlarged to approximately 40 times its normal size.

After surgery, Moore's doctor and his technician developed the "Mo" cell line from a sample of Moore's spleen obtained from the pathologist. These scientists found the "Mo" cell line produced high quantities of a variety of interesting and potentially useful proteins. In 1979, the university applied for a patent on the cell line, and in 1984, the U.S. Patent and Trademark Office (PTO) granted a patent naming the scientists as inventors, with rights assigned to the university. Even before receiving the patent, the university, on behalf of the scientists, entered into a 4-year collaborative research arrangement in 1981 with two biotechnology and pharmaceutical companies for exclusive use of the "Mo" cell line.

After his splenectomy, the doctor obtained blood samples from Moore over the course of several years. In 1983, Moore initially signed a research consent form waiving any claims to results from the research and giving the university all rights to products. On a research consent form signed at a later date, however, Moore refused to waive his rights to any products developed from his blood.

In 1984, Moore filed a lawsuit claiming his blood cells were misappropriated, and that he was entitled to share in profits derived from commercial uses of the “Mo” cell line and any other products resulting from research on any of his biological materials. In March 1986, the trial judge dismissed Moore’s complaint as failing to state a legally cognizable claim, and in 1990 the California Supreme Court rejected his appeal (In re Moore, 1990).

The National Institutes of Health’s DNA Patent Application

Until summer 1991, as scientific advances in human genetic research incrementally progressed, researchers, universities, and biotechnology companies filed and received a range of human DNA sequence patents on genes and their products--for diagnostic, therapeutic, or research purposes (ch. 3). In June 1991, however, many felt this orderly process, or at least one perceived as orderly, was altered when NIH sought intellectual property protection on more than 6,000 short sequences of human DNA (ESTs) that, by the nature of their isolation method, coded for putative human genes and therefore human proteins, but were themselves incomplete gene sequences. The patent application was made possible by the development of a rapid gene sequencing technology (Adams, 1992), a process for which NIH also initially sought patent rights, but subsequently dedicated to the public.

The outcry that followed the public disclosure of the NIH maneuver was swift and predominantly negative (Adler, 1992a,b; Aldhous, 1992; Anderson, 1991; ASHG, 1992; Cook-Deegan, 1994; Curien, 1992; Eisenberg, 1992; OSTP, 1992; Healy, 1992; HUGO, 1992; Riley, 1992; McKusick, 1992; Pompideau, 1993; Roberts, 1991, 1992a,b). Though the human DNA sequences encompassed by the NIH application were acknowledged to be fragments of genes, the application

included broad claims to the entire putative gene and its protein product. Never before had such broad-based and far-reaching claims for so many human-derived products been sought by a single applicant, irrespective of the fact--though not insignificant--that the sequences disclosed were not for complete genes nor individually associated with specific biological functions. Moreover, because the U.S. Government filed the application, a process largely conducted in secret (i.e., the evaluation of a patent application (ch. 3)) was opened to public scrutiny and debate--a situation acknowledged by both opponents and proponents as desirable, especially once similar actions by the private sector came to light (Anderson, 1993).

In fall 1992, NIH announced that PTO had rejected NIH's initial application (as it does for most first applications, which tend to seek the broadest possible scope of coverage.) PTO held the NIH application lacked novelty, utility, and was obvious. NIH responded to PTO's initial rejection in February 1993, modifying the claims, but the PTO examiner again rejected the application. A year later in February 1994, facing a deadline to appeal the rejection to the Board of Patent Appeals and Interferences (a review body within PTO) or the Federal courts, NIH withdrew the entire application. Nevertheless, its legacy challenged conventional thinking about strategies for seeking patents on human DNA sequences, spotlighted the role of Federal technology transfer in biotechnological innovation, and underscored the perception of the pivotal impact of that molecular medicine will play in ameliorating disease.

THE INTERESTED PARTIES

If human DNA sequence patents have been granted prior to the NIH application, why did controversy arise and who are the stakeholders? Once the NIH action was revealed, disagreement among patent attorneys as to whether patent law supported granting such an application immediately erupted. Within the Federal Government, the two principal agencies funding human genome research--NIH and the Department of Energy--sought to reconcile distinct opinions, and the two trade associations then representing the biotechnology industry staked different positions. International

opposition--represented by governments, professional organizations, and individuals--also was expressed. Likewise, academic researchers and professional societies in the United States voiced initial opposition (OSTP, 1992).

The vast majority of stakeholders opined that regardless of the merits of the NIH application, patents were important to foster innovation in biotechnology. What is indisputable is that common to the disparate perspectives was the sentiment that public debate was welcomed. And underlying the wrangling, posturing, and positioning was the knowledge that potentially at stake were billions of dollars (Spalding, 1993; Korman 1994; Burrill, 1993).

THE PROBLEM OF UNCERTAINTY

The past decade's confluence of biotechnology and patents has produced a surge of litigation, as companies seek to enforce their rights against infringement and defend the patent grant in opposition or revocation proceedings. Such litigation is not surprising, given the web of partially overlapping patent claims, the potential high-value products, the problem of prior publication., and the fact that many researchers and companies are interested in the same products. Additionally, because biotechnology is a relatively new area in patent law, litigation is not unexpected. Thus, how PTO and the courts interpret biotechnology patent claims will continue to be an issue in the next few years. Uncertainty over patent rights can be costly and might affect the way biotechnology companies structure their research and development portfolios.

Although NIH has withdrawn its EST patent application, the problem of uncertainty remains. On the one hand, the NIH withdrawal is viewed positively by those who argue that the Federal Government should not be in the business of seeking patents on such early stage research results. Additionally, NIH will not expend tax payer funds pursuing a patent application that its leadership, which underwent a change since the application was first filed, believed was fundamentally flawed. Still, commercial ventures have proceeded with similar applications, and discussions surrounding the

scope and nature of the claims sought by these applications will be, as with any other patent action, confidential matters between the applicant and PTO. Unless a patent issues from one of these applications, or until an applicant files a court action, the prospect of uncertainty remains real and any indication of the direction of resolution stays secret. Thus, others believe NIH lost an opportunity for leading continued public discourse on the advantages or disadvantages of EST patents, but more importantly forfeited the chance to shape any precedent that might be set by a vigorous pursuit of the application.

The NIH patent application also highlights the tension that exists between law and science. A clear majority of researchers expressed to OTA the belief that PTO should not grant composition of matter patents for ESTs (OTA, 1993b; ch. 5); whether the applicant is the U.S. Government or a private party is immaterial to these individuals. With respect to putative gene sequences, knowledge about the protein and its role in vivo are the information scientists usually seek, although certainly they confirm the benefit of knowing the genomic location of a putative gene, its potential as a DNA diagnostic and, in the future, the potential of a DNA sequence per se as a therapeutic.

Most scientists oppose the patenting of ESTs, however, on the belief that the amount of effort expended making the invention does not justify a scenario whereby an EST patent holder receives proprietary rights that may dominate the rights of a scientist who elucidates and characterizes the in vivo function of the gene and gene product. Even if a full gene sequence is elucidated, as will increasingly become the norm, in the absence of further characterization of in vivo function, many researchers believe it unfair to allow patents on the results of such automated DNA sequencing, since the intellectual effort involved generally is less than for functional characterization. Hence, if PTO disallows patents on these types of sequences, companies or other parties might opt to maintain their DNA sequences as trade secrets until their research reaches the stage at which they are comfortable that PTO will issue a patent; publishing such sequences (or making them widely available through public databases) prior to that point could jeopardize the opportunity of that company or individual--or even a competitor working on the same gene--to obtain a composition of matter patent and reap

future rewards. In contrast, when patents are granted, the inventor must make a public disclosure about the subject matter.

Patent law's purpose, however, is to promote the progress of science and the useful arts, not necessarily to reward hard work with intellectual property rights while disallowing patents for that discovered through minimal labor. Just because it is easy to do does not mean it is not patentable. Hence, patent lawyers, on behalf of their clients--the biotechnology industry, universities, and scientists--will continue to seek the broadest protection possible for genome-derived patents; to do otherwise breeches the fiduciary duty, but perpetuates the tension between the science and law.

Finally, opponents of EST-like patents worry about the prospects and potential consequences of allowing human DNA sequence patents en masse. If granted en masse, EST patents (or gene patents not fully characterized with respect to in vivo function) with broad claims to the entire gene and gene products could effectively place control for development and profit of thousands of genes into the hands of a single patentee--a notion many find objectionable, but with no foundation in patent law per se.

Overall, academic researchers, as well as companies, face uncertainty over whether they will be able to secure clear title to rights on work they perform to characterize a particular gene. Despite this potentially adverse impact, however, OTA found a majority of academic molecular researchers surveyed believed that even if the NIH application had been granted, their research would be unaffected--though a majority speculated that the research of their colleagues would be adversely affected (ch. 5). And, although the biotechnology industry--probably the stakeholder most affected by problems of uncertainty--expressed vocal opposition or consternation when NIH initially filed its applications, the passage of time has muted concerns about the uncertain future. By early 1994, OTA found most biotechnology companies willing to accept uncertainty until PTO or court decisions issue and unwilling to consider changes to U.S. patent law (OTA, 1994).

It is impossible to state categorically whether any single, pending human DNA sequence patent application of the NIH type will stifle or enhance research and development of new diagnostics and therapies. Patents on ESTs, an early stage development compared to fully sequencing and characterizing in vivo function, might reduce the reward--and hence, incentive--for the developments and improvements that bring biotechnological products to consumers. On the other hand, allowing patents on ESTs or complete gene sequences of unidentified in vivo function fosters dissemination, could accelerate commercialization of valuable genome-derived products, and could facilitate the construction of a human genome map. From a policy perspective, striking a balance that optimizes such trade-offs is key.

THE OTA ASSESSMENT

The NIH filing sparked renewed interest in longstanding debates (Kevles, 1993) about the role of patents in technology transfer and their impact on biomedical research (Eisenberg, 1993; Krinsky, 1991; Grinnell, 1992, 1993; Jones, 1986; Korn, 1987; Nader, 1993; Nelsen, 1993; Newbower, 1993; OTA, 1988a,b, 1989 Payne, 1988; Witt, 1994). Still, though the NIH move catalyzed today's debate (Adler, 1992a,b; Aldhous, 1992; Anderson, 1991; ASHG, 1992; Cook-Deegan, 1994; Curien, 1992; Eisenberg, 1992; OSTP, 1992; Healy, 1992; HUGO, 1992; Riley, 1992; Pompideau, 1993; Roberts, 1991, 1992a,b), the issues raised extend beyond the NIH applications. Thus, while the NIH application sparked widespread debate about intellectual property protection and the Human Genome Project, in some respects the debate reflects several pre-existing concerns:

- Who can obtain and assert exclusive proprietary rights to human DNA sequences or other human biological material?
- What social and ethical issues are raised by patents on human DNA sequences, and what Federal mechanism exists to consider them?
- Has the trend to commercialize biomedical research results, generally, affected the academic research enterprise?
- What impact have technology transfer laws had on biomedical research, generally and the Human Genome Project, specifically?

Concern about these questions led Senator Edward M. Kennedy, Chairman, Committee on Labor and Human Resources; Senator Mark O. Hatfield, Ranking Minority Member, Committee on Appropriations; and Senator Dennis DeConcini, Chairman Subcommittee on Patents, Copyrights, and Trademarks, Committee on the Judiciary to request this Office of Technology Assessment (OTA) report (Hatfield, 1993; Kennedy, 1993; OTA, 1993; box 2-D). Stemming from its oversight and appropriations role for the Human Genome Project, Congress has an ongoing interest in a range of issues related to human genetics and applications of DNA technologies (OTA 1984b-92). The request also reflects longstanding congressional interest in the commercialization of biomedical research and the role of biotechnology in economic competitiveness (OTA 1981, 1984a, 1988b, 1991b).

OTA Surveys

In collecting information for this assessment, OTA found specific details were needed to answer several questions covered by the report:

- How many patents that involve human DNA sequences (or, for example, claim human applications based on presumed similarity with a characterized mouse DNA sequence) has the PTO granted? What types of patents are these? For what types of applications? Have the claims changed qualitatively over time? Who are the assignees and have they changed over time?
- What have been university and research institutions' experiences since the enactment of Federal laws to enhance technology transfer? How many patents? What type of licensing is most common? How much income? What obstacles repeatedly arise? From their perspective, what measures, if any, could the Federal Government adopt to improve technology transfer?
- What has been industry's experience with collaborative arrangements involving NIH or DOE? How do they originate? What outcomes have been produced? Does industry view them as successful? From their perspective, what measures, if any, could the Federal Government adopt to improve technology transfer?
- How do scientists perceive the commercialization of genetic research? How do they view the NIH patent applications? Has sensitivity to the increasing importance of intellectual property protection of their research altered their research practices? Have there been effects on collaboration? On publication? Transfer of information or

materials? How many have patents? How many are involved in research partnerships with industry?

- Are there relationships between publication, citation, patenting and Federal laboratory technology transfer activities? Are NIH scientists who are involved in formal collaborations with industry more likely to hold patents? Is there a relationship between scientists who are involved in formal collaborations with industry and publication and citation frequency? Are NIH scientists who hold patents more, or less, likely to publish or be cited¹?
- What have been university and research institutions' experiences since the enactment of Federal laws to enhance technology transfer? How many patents? What type of licensing is most common? How much income? What obstacles repeatedly arise? From their perspective, what measures, if any, could the Federal Government adopt to improve technology transfer?
- What has been industry's experience with collaborative arrangements involving NIH or DOE? How do they originate? What outcomes have been produced? Does industry view them as successful? From their perspective, what measures, if any, could the Federal Government adopt to improve technology transfer?

OTA addressed the lack of data by conducting five lines of empirical research in these areas.

The following sections briefly summarize the scope of the five OTA surveys. Data are presented in the chapters that follow; details related to methodologies are reported in appendixes A, B, and C.

Analysis of Human DNA Patents

In 1980, two events pivotal to today's controversy occurred. The University of California, San Francisco and Stanford University received a patent for the basic technique underlying genetic engineering, and the U.S. Supreme Court held that a live, human-made microorganism is patentable. To assess how patents involving human DNA sequences have evolved since then, PTO provided OTA with the full text of patents involving or encompassing human DNA. OTA then analyzed the patents along several parameters.

¹ Contract work related to these questions is in progress, and so data are not presented in this draft. Members of the Advisory Panel will review this material prior to the report's delivery to Congress.

Survey of Researchers

One of the most vocal sectors opposed to the NIH EST patent filing was the academic-based researcher. Thus, to gauge the attitudes of scientists toward the NIH application specifically, as well as intellectual property and technology transfer issues generally, OTA surveyed 253 randomly selected recipients of NIH grants awarded through study sections principally funding grants in human molecular biology. Additionally, OTA sought information to assess the impact, if any, of these patents and technology transfer on research practices.

Bibliometric and Patent Analysis

Publication counts and citation analysis are part of the field of bibliometrics, an indicator of research productivity, although it does have limitations (OTA 1988a, 1991; Edge, 1979; Cozzens, 1981; Garfield, 1979; Narin, 1976). To explore relationships between publications, citations, patenting, and Federal technology transfer activities, OTA conducted a bibliometric and patent analysis of intramural NIH scientists participating in one or more CRADAs compared to NIH scientists not involved in CRADAs.

Survey of University Technology Transfer Offices

To address questions related to technology transfer, OTA sought data related to the experiences and perspectives of university technology transfer officials. Questionnaires were mailed to institutions that fell within the top 40 in funds received from either NIH or DOE life sciences or both.

Survey of Biotechnology Companies

In November 1993, OTA surveyed 100 biotechnology firms by telephone to assess their experiences with a technology transfer mechanism called Cooperative Research and Development

Agreements (CRADAs). Firms involved in NIH or DOE life sciences CRADAs were contacted and compared to a sample of firms not involved in CRADAs.

Scope and Organization

This report focuses on issues arising from patenting human DNA sequences. Chapter 1, which precedes this introductory chapter (ch. 2), summarizes the entire report, presents the key findings, identifies the Federal policy issues related to the Human Genome Project and patenting human DNA sequences, and analyzes congressional options to address these issues. Chapters 3 through 6 analyze four key aspects related to the commercialization of human DNA sequences: patenting issues, ethical considerations, research and development implications, and Federal technology transfer. Appendixes A, B, and C describe the methods for OTA's analysis of human DNA patents; OTA surveys of university technology transfer offices, biotechnology companies, and genome researchers; and OTA's bibliometric and patent analysis, respectively.

This report does not analyze the potential impact of patenting nonhuman DNA sequences. Many issues identified in this report apply generically in considering intellectual property protection of DNA from other sources (e.g., plants or animals), and they especially pertain to patenting DNA from model genome organisms (e.g., yeast, fruit fly, or mouse) where public expenditures are involved. Nevertheless, several aspects differ, for example ethical considerations of patenting plant or animal DNA. Similarly, because federally funded research for plant and animal genomics chiefly funnels through the U.S. Department of Agriculture, technology transfer issues would be distinct. Issues related to international collaboration might also differ, since arguably a greater range of countries are involved in plant genetics research than the Human Genome Project. Exploring such differences, however, was not possible for this assessment.

Also beyond the scope of this report is an evaluation of the Human Genome Project per se and the use of information derived from it; OTA has analyzed applications of genome research elsewhere (OTA, 1984b-92).

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Box 2-A -- What is DNA?

Deoxyribonucleic acid (DNA) is a chemical molecule that serves as the repository of genetic information in most living organisms. Its structure resembles a twisted ladder, referred to as a double helix (figure 2-1) and consists, in part, of four chemical subunits commonly called bases. These four bases--guanine (G), adenine (A), thymine (T), and cytosine (C)--are the genetic alphabet. The bases pair predictably--A with T, and G with C--to form the DNA double helix structure, and scientists refer to each pairing as a base pair, which serves as the fundamental measure of a DNA fragment's size.

The unique linear order of bases--i.e., the sequence--in the DNA helix serves as the blueprint for an organism. Put differently, the sequence of bases distinguishes one segment of DNA from another, and any function that can be assigned to a particular stretch of DNA derives from the precise order of bases. In vivo, the human genome is comprised of millions of bases contiguously arrayed in organized bundles called chromosomes (figure 2-2).

Lengths of DNA ranging from fewer than 1,000 to 2 million base pairs comprise a gene, the fundamental physical and functional unit of heredity. About 50,000 to 100,000 structural genes--i.e., DNA stretches encoding protein products--are scattered among a matrix of DNA bases that do not encode a protein. In total, over 3.3 billion base pairs constitute the human genome. Changes, or mutations, in human DNA sequences can lead to genetic disease. For example, a single base change in the gene for hemoglobin, a blood component, causes red blood cells to sickle.

The bridge between DNA's chemical information and physical realization of its instructions consists of steps that convert the DNA code into biological products. Through a process called gene expression, a DNA sequence for a structural gene ultimately results in formation of a molecule called a protein (figure 2-3); the DNA sequence determines the composition and nature of the protein product. Proteins are required for the structure, function, and regulation of all cells, tissues, and

organs in the body. Blood proteins, for example, coagulate or dissolve blood clots. Other proteins mediate physiological responses such as digestion or sugar metabolism.

In the first step in gene expression, the bases of a DNA sequence are copied, or transcribed, into messenger ribonucleic acid (mRNA). Following transcription, additional reactions translate the mRNA sequence into the protein product. Thus, the path from code to product typically involves two major steps: DNA to RNA to protein, with the possibility of modifications at each step. The range of mRNAs, and hence proteins, can differ among cell types--e.g., between brain cells and liver cells.

Scientists can isolate segments of DNA in vitro and determine the sequence of bases. Additionally, scientists can isolate mRNAs and artificially reverse the general reaction of mRNA to DNA in order to create in vitro a copy in the form of a DNA sequence (so called cDNA).

Knowing the precise order of the bases does not necessarily equate with knowledge of-the DNA segment's in vivo function. Conversely, knowing only a fragment of a gene sequence can provide scientists with enough information to assign a putative role in vivo. Moreover, a DNA sequence need not code for a gene product to be useful commercially or in research; the order of bases in and of itself can be valuable. Unique stretches of DNA sequences can serve as markers for disease genes, and hence be used as a diagnostic tool. Other fragments, for which scientists can only speculate about an in vivo function, are useful for paternity or forensic identification (OTA, 1990a).

SOURCE: Office of Technology Assessment, 1994.

Box 2-B -- What is a Patent?

Biotechnology--both as a scientific art and business enterprise--is only 20 some years old. Modern uses of molecular technologies have captured the imagination of scientists, financiers, policymakers, journalists, and the public. Still, while many issues surround biotechnology and molecular genetics are new, the concept of patents is not. Now over 200 years old, U.S. patent law derives from the Constitution and has proved itself a durable incentive for the creation of millions of inventions. The recent interface of biotechnological products and patent law, however, has raised several policy issues (Gough, 1991; OTA, 1989; OTA, 1991b).

Though chapter 3 presents details on patent law and patentability of biotechnology products, it is important at the outset to understand some basic elements of what a patent is and what it is not. In the United States, the Patent and Trademark Office (PTO) issues patents, which grant the patent owner a temporary right to exclude all others from making, using, or selling an invention during the term of the patent. In the United States, a patent may issue to anyone who invents or discovers a new and useful process, machine, manufacture, or composition of matter, or a new and useful improvement thereof. A patent, however, is not a license for its owner to make, use, or sell the invention. The use of patented products, like the use of other kinds of property, may be regulated by Federal, state, or local law. Differences exist among nations regarding intellectual property protection of inventions, including what constitutes patentable subject matter (OTA, 1991b). U.S. patent law is the broadest and most inventor-friendly statute in the world.

The rationale behind patent law is simple: To foster and reward innovation, the Federal Government guarantees inventors a temporary monopoly on their inventions to justify the risks of development, and so they can pursue a profit. In return, the patent holder discloses how the invention works so that the knowledge is available to the public for others to build on. To secure a patent, the subject matter must have utility, be novel, and be nonobvious to someone similarly skilled in the art.

SOURCE: Office of Technology Assessment, 1994.

Box 2-C -- The Human Genome Project

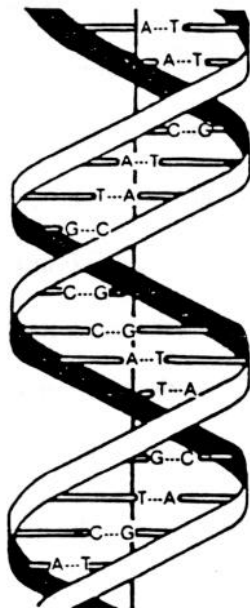
In humans, as in essentially all forms of life, deoxyribonucleic acid--DNA--contains the entire genetic blueprint for an individual. Currently, scientists in the United States and abroad have committed to elucidating the details of this blueprint, or genome. In 1985, the Human Genome Project--an estimated 15-year, \$3 billion initiative--emerged as an ambitious effort to identify the location and composition of the 50,000 to 100,000 human genes (the fundamental units of inheritance) (Botstein, 1985). The project has been undertaken with the expectation that enhanced knowledge about genetic disorders, increased understanding of gene-environment interactions, and improved genetic diagnoses can advance therapies for the 5,000 or so currently recognized human genetic conditions; a premise supported by the fact that even prior to formal launching of the project, advances in medical genetics were instrumental in the development of new therapeutic approaches (Botstein, 1980; Cook-Deegan, 1994; NRC, 1988; OTA 1988a).

Progress in understanding human genetics can aid drug development by defining specific subpopulations of patients, thus simplifying the process of ascertaining the efficacy of new drugs. Another promising treatment strategy the Human Genome Project might accelerate is gene therapy--deliberately introducing genes into human cells to compensate for aberrant genes that cause genetic disease. In the future, DNA itself could serve as a therapeutic agent (OTA, 1991b; OTA, 1993a).

Still, molecular genetics research constitutes only one of many approaches to alleviate disease (Strohman, 1994). Following the trail down to the DNA sequence cannot even fully explain many classical genetic diseases, and clearly genetic factors are only a part of most major diseases. The attraction of the Human Genome Project and genetic approaches to disease, however, is that molecular technologies are so powerful. Most major diseases have been studied for decades. Those more readily explained by traditional approaches have yielded; molecular biology offers a strategy to crack those that have not.

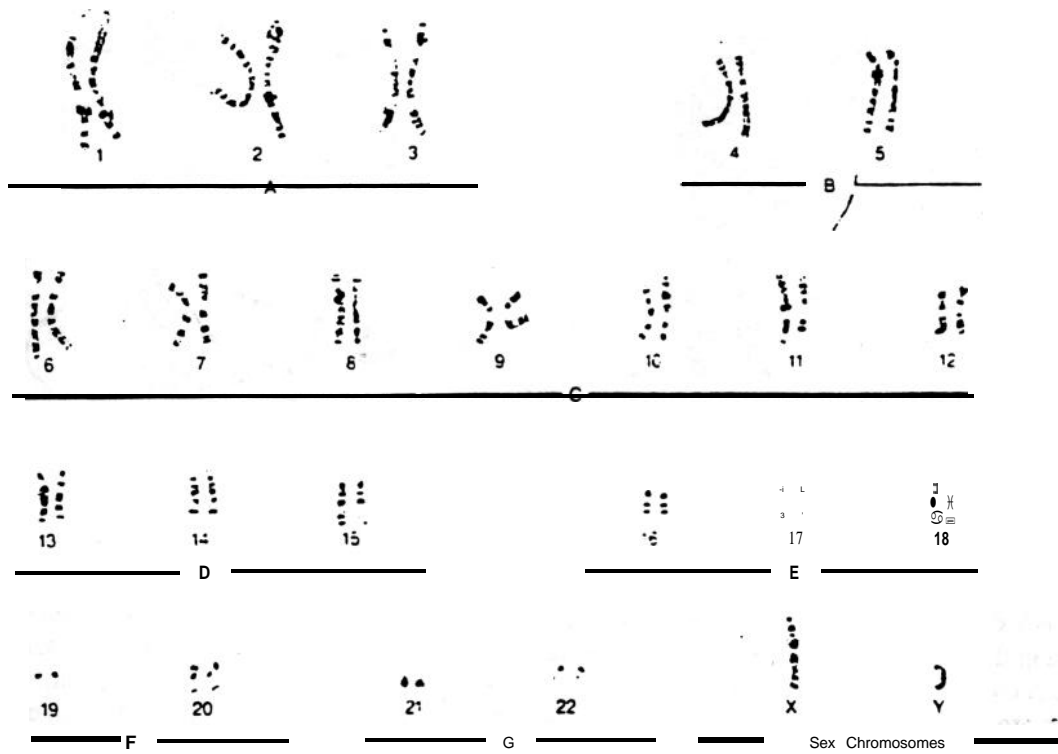
SOURCE: Office of Technology Assessment, 1994.

Figure 2-1 -- Structure of DNA



SOURCE: Office of Technology Assessment, 1994.

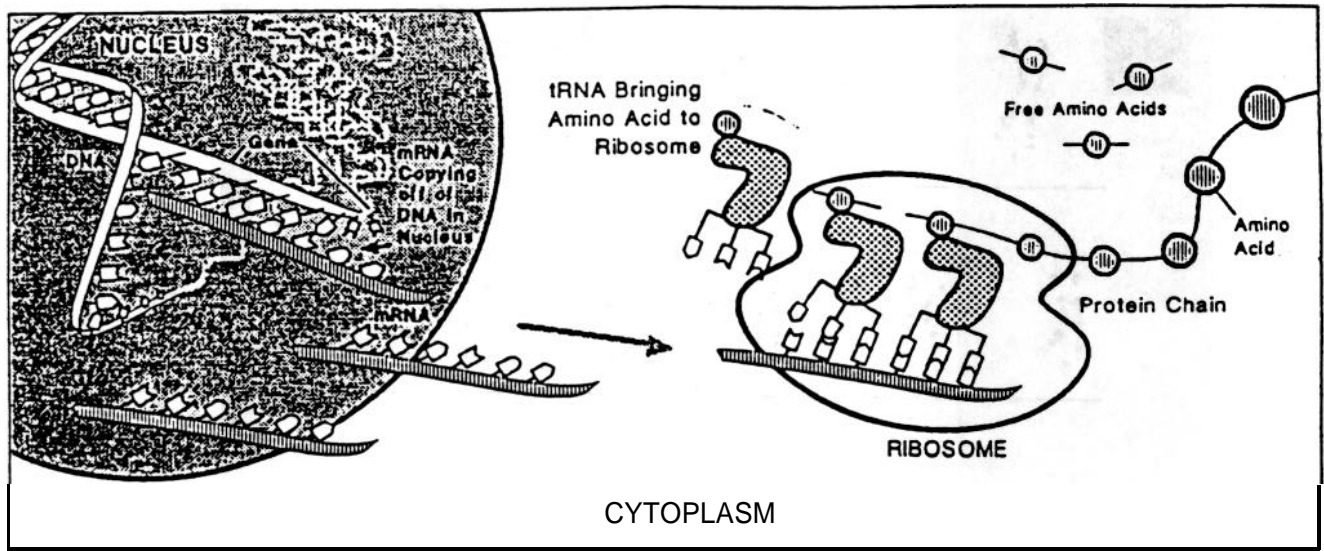
Figure 2-2 -- Human Chromosomes



DNA is associated with protein in organized microscopic bundles called chromosomes. Humans have 46 chromosomes; 1 pair of sex chromosomes (two X chromosomes for females; an X and a Y for males) and 22 pairs of autosomes. The entire genetic package is referred to as the human genome.

SOURCE: IG Laboratories, Santa Fe, NM, 1992.

Figure 2-3 -- Gene Expression



In the first step of gene expression, messenger RNA is transcribed from DNA. In higher organisms, this process takes place in the nucleus of a cell. In response to certain signals, sequences of DNA adjacent to, or sometimes within, genes control the transcription to mRNA. The second major step in gene expression involves translating the mRNA sequence into a protein product. mRNAs are known as such because they carry messages specific to each of the 20 different amino acids that generally make up proteins. Once synthesized, mRNAs leave the nucleus of the cell and migrate to another cellular compartment, the cytoplasm, where their messages are translated into the chains of amino acids that make up proteins. A particular sequence of three bases in the mRNA codes for an amino acid, and the main component of the translation machinery is the ribosome--a structure composed of proteins and another class of RNAs, ribosomal RNAs. The ribosome reads the genetic triplet code of the mRNA, while a third RNA molecule, transfer RNA (tRNA) effects protein synthesis by bringing specific amino acids to the ribosome for attachment to the growing amino acid chain until the full protein is synthesized and released from the ribosome.

SOURCE. Office of Technology Assessment, 1994.

CHAPTER 3

PATENT ISSUES

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As the 21st century approaches, Congress and the executive branch have committed to funding scientific research and technological developments to determine the location of all human genes. This federally coordinated effort of research into our genetic makeup, the Human Genome Project, has raised society's awareness of a new era of legal and social issues. Simultaneously, legal and political trends reinforce the increasing importance of intellectual property protection to parties conducting genome research. Today, one of the oldest and most stable areas of U.S. law--patent law--is being called upon to mediate at the frontier of these issues and trends.

WHAT IS A PATENT?

A patent is an exclusive right granted by the government to the inventor to exclude others from making, using, or selling the invention. The foundations of patent systems, which induce inventors to contribute something useful to society by providing the incentive of exclusivity in exchange for public disclosures of inventions are based on early Venetian law. The Venetian Senate's 1474 Act established a legal system under which patents were granted (Merges, 1992). "Patent" comes from the Latin *patere*, meaning to be open and referring to an open letter of privilege from the sovereign. The moral justification of the patent system is premised on a social contract between an inventor and society for a limited period of time. Under this social contract society has access to the creative fruit of inventors and inventors receive the sole right to exclude others from using and developing the invention as both an inducement for, and reward for the contribution. Thus the social benefits of technological progress are achieved by means of private rewards (Merges, 1992).

The patent system is one of the oldest institutions in the United States. Article I, Section 8 of the U.S. Constitution grants Congress the power "[T]o promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." Acting on the constitutional grant of authority, Congress passed the first Patent Act in 1790, which provided the basic concepts we associate with patents today, exclusivity, novelty, utility and inventiveness. Our current patent system was established by the 1952 Patent Act,

which codified approximately 150 years of incremental development on the basic patent system established in 1840.

Since the inception of the patent system, an office has been devoted to the examination of patent applications. In the early 1800s, the Patent Office was formally established and based in the State Department. Early this century, the Patent Office was transferred to the Department of the Interior, and subsequently to the Department of Commerce. Presently, the Patent and Trademark Office (PTO) is an agency of the Department of Commerce, and serves the function of examining patent applications and granting patents.

The patent system serves to balance the public's interest in access to information on inventions and the inventors' interests in receiving compensation for their efforts. Patent law grants patent holders exclusionary rights for a limited time to encourage innovation, induce public disclosure of inventions, and encourage the investment of time, money, and creative energy by the inventor. A U.S. patent allows the patent holder to sustain a monopoly by conferring the right to exclude any other person from making, using, or selling the invention for 17 years from the date the patent is granted. In exchange for the limited monopoly, the inventor must disclose the details of the invention. Thus, the invention is made public, but the inventor controls who may practice the invention. Disclosure of the invention's details "promotes science and the useful arts" by creating the possibility of further innovation and improvement of the invention. Once the patent term expires, the invention is freely and publicly available; the inventor cannot restrict the use of the invention or charge a fee for using it, and no further rights extend to the patent holder.

Disclosure is fundamental to the policy underlying patent law. It is achieved through the publication of the patent by the Federal government. By law, the patent must include a detailed description of the invention so that someone skill in the area of expertise can recreate it. Thus, the invention is made public, but the inventor controls who may practice the invention. Disclosure of the invention's details "promotes science and the useful arts" by creating the possibility of further innovation and improvement of the invention.

Dissemination may also be achieved through licensing of the invention to others so that they may make, use, or sell it. Both disclosure through government publication and licensing promote further innovation because new experimenters may improve a previously patented invention or be inspired to develop a radically different approach to the same objective, and receive a patent for these improvements. Either way, science and industry are enriched and the public benefits from the further innovation.

Once the patent term expires, the invention is freely and publicly available for other or make, sell, and use; the patent holder has no further rights.

OBTAINING AND ENFORCING PATENT RIGHTS

The rewards and incentives of the patent system are the basis for how the patent system deals with specific inventions and discoveries. What is a patentable invention? How does one obtain patent rights? What is the nature of those rights? How does one assert and protect patent rights? The following section explores basic patent concepts and discusses how they relate to human genetic discoveries (box 3-A).

Elements of a Patentable Invention

In order to secure patent protection, an invention must meet three statutory criteria of utility, novelty, and nonobviousness. Additionally, valid patents require: a written description of the invention; an enabling disclosure that describes to a person skilled in the art how to make and use the invention; a description of the best mode for carrying out the invention; and claims which define the scope of the protectable invention.

Generally, when PTO evaluates patent applications, it does not consider safety, economic,

ethical, or social factors. Statutory prohibitions restrict the granting of patents in certain areas such as nuclear energy and nuclear weapons. PTO's professed moral and ethical neutrality stems from the absence of moral or ethical standards in the statutory framework used to determine patentability of inventions. PTO relies on its constitutionally mandated mission to "promote the progress of science and useful arts."

Utility

Utility is a fundamental requirement for a patentable invention. The utility requirement insures that the applicant has at least one provable use for an invention and weeds out impractical inventions such as perpetual motion machines, "fountain of youth" drugs, and hair restorers. In the biomedical area, "anti-cancer" drugs raise a utility issue with PTO. The utility requirement derives from a statutory provision that defines patentable subject matter as "[a]ny new and useful process, machine, manufacture, or composition of matter or any new and useful improvement" (35 U.S.C. § 101). To meet the utility requirement, the inventor must describe some utility for the invention at the time the application is filed or the utility must be self-evident. The use must be for some practical purpose and not merely finding out what the invention is good for. The utility described in a patent application does not necessarily limit the permissible scope of the patent claims, as the scope of the patent claims may extend to uses for the invention that are not yet fully realized.

In 1966, the U.S. Supreme Court held that a process to prepare a chemical compound identified only as a potential drug was not sufficiently useful to warrant patent protection (Brenner, 1966). The court said it would not "confer power to block off whole areas of scientific development without compensating benefit to the public" (Brenner at 534). According to the court, "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion" (Brenner at 536). The court rejected a lower court's standard of utility under which a process that was merely operable to prepare a chemical compound that was useful as the subject of further investigation by researchers could be patented. The court explored the policy of not granting a

patent, aware that the “inability to patent a process to some extent discourages disclosure and leads to greater secrecy” (Brenner at 533). However, the court dismissed the secrecy argument and noted that capacity for use in further research should not constitute patentable utility because, once a patent holder has the power to enforce a patent, the patent negates any incentive for others to conduct research into practical applications of the discovery (In re Joly, 1967).

These rulings present problems for biotechnology because research reagents are an industry in their own right and because EST sequence data are primarily useful only toward unknown ends.

Novelty

An inventor must claim something new to receive a patent. The precise legal definition of what is new--that is, the patent law test of “novelty” -- is contained in 35 U.S.C. § 102. In essence, this provision requires that the claimed invention has never appeared in the “prior art” in its exact form. Prior art is the technical term for all extant publications, patents, working inventions, and general knowledge as of the date of the claimed invention. Prior art consists of patents, printed publications, and evidence of public use, disclosure or sale of the invention, any of which occurs prior to the filing date of a patent application. A publication by the inventor does not preclude U.S. patent protection for an invention if the patent application is filed within one year of the publication date. Most other patent systems provide no grace period, so that any publication prior to filing a patent application can serve as a basis to deny patent protection, since it is effective as prior art.

One fundamental tenet of patent law is that products of nature in their natural state are not patentable, on the ground that they are not new. To distinguish between patentable subject matter and unpatentable products of nature one must determine “whether the claimed invention is the result of human intervention” (Eisenberg, 1990). Thus, isolated and purified proteins are patentable even though they naturally exist in an unpurified state in the human body. In an industrial sense, proteins naturally existing in the human body would be considered impure. Put into historical perspective, purified products of nature were first recognized as being patentable primarily because the invention

lay in the development of a process for isolating the product of nature in a purified form. Since process patents were more difficult to enforce than product patents, and because the purified products of nature were useful and novel materials, it was easy to conclude that the purified product of nature should be given patent protection, usually along with the process for isolating the product of nature. In a landmark case upholding a patent on isolated and purified adrenaline, the U.S. Supreme Court found that the newly purified form was novel over the natural form, and therefore deserved a patent (Parke-Davis & Co., 1912). With respect to claims to DNA, although knowing the order of bases does not confer novelty, DNA molecules containing human DNA sequences that can be protected as the isolated molecule, have cleared the novelty hurdle for patentability because an isolated sequence can be novel (box 3-B).

Nonobviousness

The third element of patentability is nonobviousness. This takes into consideration whether the information provided in the patent application would have been predictable. To meet this third requirement, the invention must not have been known or knowable by the average person trained in the same field. Thus, it calls for a comparison between the claim and prior art from the point of view of one with ordinary skill in the art. There are three factual inquiries to nonobviousness determination: 1) difference between the invention and the knowledge of the art; 2) level of skill in the art; and 3) whether the differences would have been obvious to one of ordinary skill in the art (Graham, 1966). The state of mind of the actual inventor does not matter. Unexpected results from an obvious invention may confer patentability. In assessing this requirement, PTO determines whether one skilled in the art would have been able to assemble the elements of prior art constituting the invention and would have been able to reasonably predict the outcome. PTO denies patents for inventions that would have been a predictable extension of what was known at the time the invention was made.

Disclosure

In exchange for obtaining the right to exclude others from making, using, or selling the invention, the inventor must disclose to the public through detailed description in the patent application how the invention is made and used. This is published by the Federal government when the patent is issued. The disclosure requirement encompasses three separate elements: enablement, best mode, and written description.

The enablement standard establishes the extent of disclosure requirement. In assessing whether this requirement has been met, PTO will evaluate the description provided, the character of the invention, and factors such as unpredictability, reproducibility, and the state of the art. If the invention involved living material and PTO concludes that the invention cannot be reproduced through reliance on a purely written description, PTO can require the patent applicant to make a deposit of the biological material that the public may access and use. A patent application must describe the invention in terms that are adequate to enable others to practice the invention. Every patent application must include a specification (i.e., a written statement) containing the disclosure. Additionally, the disclosure must enable one skilled in the art to make and use the invention without undue experimentation (In re Wands 1988). It must also contain a description that shows the inventor was actually in possession of the invention. Disclosures also must describe the best mode known to the inventor to carry out the invention as of the filing date. The best mode requirement is based on the knowledge of the inventor at the time of the filing. In other words, an inventor can not disclose an inferior method of practicing the invention while concealing a method the inventor knows to be the best method. Finally, disclosures must be written so that any person skilled in the art can understand the invention.

Claims

The heart of a patent is its claims, the legal language reciting exactly what the inventor considers to be the legally protectable invention. Once the patent is granted the claims are the exact rights awarded to the inventor, and as such, are the legally protected invention. In patent law, validity

and infringement turn critically on the precise wording of the claims. The specification is a general description of the invention. At the conclusion of the specification, the applicant must set forth one or more claims “particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention” (35 U.S.C. § 112). The language of the claims, more than the description of the invention set forth in the specification, defines the scope of the exclusive rights. By reading the claims, the public knows exactly what the inventor and PTO consider the extent of the inventor’s property rights. The specification may cover more areas of the technology in its description.

After examining the application, PTO may simply issue the patent, but more typically the examiner rejects some or all of the claims on a variety of grounds. The applicant may respond, either by arguing that a patent should issue on the claims as drafted or by amending the claims to overcome the rejection. This process, called patent prosecution, continues until the patent is issued or the claims are finally rejected or abandoned. Applicants may choose to modify the scope of their claims if the grounds for rejection may be overcome by amending the claim language. Disgruntled patent applicants may appeal final rejections of their claims, first to an administrative appeals board in PTO, the Board of Patent Appeals and Interferences, and then to the U.S. Court of Appeals for the Federal Circuit, or may bring a civil action against the Commissioner of Patents in the U.S. District Court for the District of Columbia.

Claims may be directed to, among other things, new compositions or new methods to use or prepare either new or old compositions. This has obvious applications where a partial DNA sequence of unknown utility is in the prior art when a use for the full sequence is later described. A patent on a new use for an old compound often will be allowed if the compound is combined with other compounds and claimed as a new combination. Protecting new use via combination claims has been allowed where the old compound is combined with a second active ingredient, or with an ingredient that enhances the effect of the old compound. Either strategy is available to inventors in the biotechnology field. New use or composition patents are less desirable than product patent protection for the basic structure, as the composition patent will be limited in scope and cannot be used to

preclude others who use the basic structure in different compositions. Again, the patent rights to the new use cannot be used to preclude others from making different uses of the structure or composition. For example, the inventor of Retin-A compound, who owns a patent with a university on use of the compound for treating acne, filed his own “new use” patent for application of the compound for fighting wrinkles (Box 3-C).

Simply because a compound is known, does not preclude the patenting of a composition of matter contain that compound if the subject matter as a whole meets all the criteria for patentability. This principle also applies to different compositions containing the same ingredient. If an invention uses an old compound or an old composition in a different way than was known, a patent may be available for a new use of the known product (process claim), but does not render the product per se patentable anew. A patent on a product gives the inventor the right to exclude others from any use of that product for the full term of the patent, whether or not the use was discovered by the inventor.

Infringement and Remedies

Anyone who, without authority makes, uses, or sells an invention defined by an issued claim infringes that claim. For example, use of an EST to identify a full gene, which is then used to express a protein product--is an infringement. In theory, even a single use of a patented DNA sequence--say, use of an EST to identify the full gene, which is then used to express a protein product--is an infringement. Clearly, then, multiple uses of a patented EST, e.g., by inclusion within an entire gene used repeatedly to express a desired protein, would be likely to constitute infringement. Any of these uses then gives the patent holder the right to an injunction against the continued manufacture and use of the full gene and its protein product. If the claims do not cover the full length gene, it is unlikely that the use of the full length would be enjoined. Thus, it is conceivable that the owner of a patent on a portion of a gene might attempt to extract royalties from subsequent researchers who identify the

full gene and its protein product. Companies or researchers using a patented DNA sequence infringe the patent, even if they are unaware that the DNA sequence has been patented; intent to infringe or awareness of the patent is not required. Regardless of intent or awareness, the researcher or company must obtain permission from the patent holder to use a patented substance or process. In this environment, where infringement has such stark consequences, much attention will be addressed to the issue of defenses. The extent to which researchers within companies or universities may infringe EST patents (if granted) or sequence patents is at the heart of the patent controversy in biotechnology.

Once a patent is granted, enforcing the patent falls to the patent holder. Enforcing a patent is costly because the patent owner must spend time and energy monitoring unauthorized users and incur considerable legal expenses pursuing those who are believed to infringe. Similarly, it can be costly for users of a patented product or process to determine if their contemplated activity would infringe the patent. Some users might fail to identify the patent or to understand correctly its scope. Others who know that the patent exists, might risk an infringement action and use the patented invention without permission if licensing the patent is too costly or is not possible, or they believed the patent invalid. There is no obligation on patent holders in the U.S. to make licenses available.

Once a patent holder discovers an infringement, action can be brought to enforce the patent rights. As a defense, the infringers may assert that the patent is invalid or that their product or process does not infringe the patent, or both. If the infringer fails to prove that the patent is invalid and the patent holder proves infringement, the court may force the infringer to cease as well as award damages for past infringement. A typical injunction orders the infringer to immediately cease making, using, or selling the offending product or process. The defense of unenforceability is distinct from a defense of patent invalidity. A court can hold a patent unenforceable if it discovers that the inventor engaged in fraudulent or inequitable conduct before PTO in obtaining the patent. This defense does not address whether the claims are valid or invalid; it simply precludes the patent owner from enforcing the patent right.

In deciding whether infringement has occurred, a court must determine the technological scope of the patent claims. As an initial matter, this involves reading and interpreting the plain language of the patent claims in light of their meaning commonly understood by people working in the field of the invention. The claim is also interpreted in view of the specification, prior art, and the prosecution file history. Literal infringement occurs when the defendant's product or process falls within the scope of the claim language, even if the court concludes that there has been no literal infringement, the defendant may still be held liable for infringement under the doctrine of equivalents.

Doctrine of Equivalents

The doctrine of equivalents expands the scope of a patent's claims beyond its literal boundaries (Merges, 1993a) and is intended to prevent abuse (Craver Tank, 1950). If the patent owner cannot establish literal infringement of the patent, he or she may be able to obtain a finding of infringement through the doctrine of equivalents. Conversely, the reverse doctrine of equivalents (box 3-D), which is far more rarely applied, results in noninfringement of claims that otherwise would be literally infringed if the accused product or process is too different from that described. It leads to findings of noninfringement of claims that otherwise would be literally infringed, in effect restricting claims to the specification described, which could be a narrower scope than the literal language of the claim would suggest (SRI International, 1985).

The doctrine of prosecution history estoppel limits the doctrine of equivalents. In legal terms, estoppel prevents a person from contradicting his or her previous assertion. This doctrine prevents the patent holder from using the doctrine of equivalents to expand the scope of the claims to recover subject matter that was surrendered during prosecution of the patent application in order to get the patent issued under circumstances determined for each case. Thus, if a patent application as initially filed includes broad claim language that would have literally covered the defendant's product, but the applicant narrows the scope of the claims in a manner that excludes the defendant's product in order to overcome PTO's rejection of the broad claims based on prior art, the patent holder will be precluded

or “estopped” from later using the doctrine of equivalents to bring the defendant’s product or process within the scope of the claims in an infringement action. In some biotechnology patent cases, the courts have denied motions for summary judgment of noninfringement and allowed patent owners to present their arguments to the trial courts on whether similar products infringed, based on the doctrine of equivalents (Genentech, Inc., 1990).

One way the doctrine of equivalents might become relevant to an infringement action involving patents on human DNA sequences is if an infringer takes advantage of the degeneracy of the DNA code to substitute functionally equivalent codons in a patented DNA sequence. Application of the doctrine of equivalents would ensure that such an inconsequential substitution prevents the infringer from avoiding liability. On the other hand, if the patent applicant initially included broadly worded claims covering all allelic variations on an identified sequence, and later deleted the reference to allelic variations in response to a rejection from PTO on the ground that these broad claims had not been enabled, the doctrine of prosecution history estoppel might prevent the patent holder from using the doctrine of equivalents to effectively expand the scope of the patent to recover the subject matter that was surrendered during review of the patent application.

Blocking Patents and Improvement Patents

What if genome researchers discover a new use for a patented DNA sequence? At least two distinct situations are possible. First, where different parties have patent rights on different aspects of the same general invention (e.g., patents on different ESTs to a single gene); second, where one party has a dominant patent and one party has a subservient patent. Two patents are said to block each other when one patent holder receives a broad patent on an invention and another subsequently obtains a narrower patent on some improved feature of that invention. The broad patent is said to “dominate” the narrower one. In such a situation, the holder of the narrower, subservient patent cannot practice the invention without a license from the holder of the dominant patent. At the same time, the holder of the dominant patent cannot practice the particular improved feature claimed in the

narrower patent without a license.

Two aspects of this situation could seem counterintuitive. First, that the subservient patent may be issued by PTO, given the existence of the broad patent in the prior art; and second, that once the subservient patent was issued the holder of the dominant patent would be prevented from practicing an invention that clearly falls within the scope of the initial claims. Subservient patents can be issued, however, when they disclose an improved feature that meets the statutory tests of novelty and nonobviousness. Even though the subservient patentee invents a nonobvious variant of an invention covered by a broad patent, the broad patent is not invalid for lack of enabling disclosure under 35 U.S.C. § 112 (*Amerace Corp.*, 1982). A subservient patent can prevent a dominant patent holder from practicing the particular improved feature claimed in the subservient patent because patents grant the right to exclude, not the right to practice an invention. (See 35 U.S.C. § 154). Thus, the dominant patentee can exclude the subservient patentee from practicing the invention at all; and the subservient patentee can exclude the dominant patentee from practicing the specific, improved feature (*Cantrell & Co.*, 1986). Issuance of an improvement patent, and a holding that a patent is valid but subservient to another patent, can both create blocking patents. Clearly, it's preferable for an inventor to own a patent free and clear of anyone else's claims, and so an inventor usually does not characterize an invention as subservient. But, a court may do so in the course of litigation. Where the court upholds the validity of an accused infringer's patent on some enhanced feature (such as a new use), but nevertheless finds that the accused product infringes a prior, broad patent, the court in effect makes the accused infringer's patent subservient to the broad patent. Of course, it is also possible that an infringing product will not qualify for its own patent.

Even where a court finds a patent subservient to another--thus creating blocking patents--the holder of the subservient patent is still better off than if he or she had never filed a patent application at all. The holder of the subservient patent can exclude the holder of the broad patent from practicing the improvement. The ability to exclude the holder of a dominant patent from practicing the improvement provides some bargaining leverage to obtain a license. The creator of a new use for a

previously patented gene sequence is well advised to obtain a patent. While it does not of itself permit that inventor to go forward with commercialization, it certainly gives him or her a strong bargaining chip in negotiating a license with the dominant patent holder. Economic motivations generally provide an impetus to cross license inventions and allow both parties access to the improved discovery. Further, the subservient patent will typically continue in force for some years after the dominant patent expires, giving the second patent holder a unique and unrestricted patent monopoly for the remaining period.

As discussed earlier, one goal of the U.S. patent system is to encourage innovation and the development of alternative technologies. The disclosure of a patented discovery is intended to serve as a stepping stone for further innovations. In fact, improving a patented product has been expressly encouraged by the courts. “Designing new and possibly better or cheaper functional equivalents is the stuff that competition is made of and is supposed to benefit the consumer. One of the benefits of a patent system is to allow an inventor . . . to ‘design around’ a competitor’s products, even when they are patented, thus bringing a steady flow of innovation to the marketplace” (State Indus., 1985; Read Corp., 1992). On the other hand, determining if a patented invention sufficiently designs around the original patent to avoid infringement can be difficult.

Experimental Use Defense to Infringement

The most relevant infringement defense in the sequence patent debate involves the experimental use exception. Dating back to a 1813 case that recognized an exception for parties to use a patented product or process in an experiment “for the sole purpose of gratifying a philosophical taste, or curiosity or for mere amusement” (Whittemore, 1813). According to this doctrine, which principally derives from case law, pure research activities using a patented invention, though technically infringements, are excused from legal liability (Eisenberg, 1989). While in theory a common sense exception to the broad sweep of patent law’s strong property rights, this doctrine is very rarely successfully raised as a defense in patent infringement cases (Eisenberg, 1989).

Of particular interest to scientists, the exception is very narrow. U.S. courts have held that making and using a patented invention in a research program is an infringement if the research is undertaken to develop a commercial product (Pfizer Inc., 1982). Research with a commercial impact does not qualify for the exception. This imposes a serious limitation on biotechnology research, where the lines between pure and commercial research often blur (Roche Prod. Inc., 1984). One such narrow holding was reversed by statute.

In *Roche Product Inc. v. Bolar Pharmaceutical Co.*, Hoffmann LaRoche held the patent on the active ingredient for a drug. Bolar wanted to manufacture a generic version of the drug that could be marketed as soon as Roche's patent expired, and began obtaining data for FDA approval on its generic version during Roche's patent term. Roche sued Bolar for patent infringement, and the Court of Appeals for the Federal Circuit, reversing the lower court, held that the experimental use defense did not cover Bolar's activities because the research had been undertaken for commercial purposes (Roche at 863, 1984). The court also said that the experimental use exception is "truly narrow"; a broad rule would "allow a violation of the patent laws in the guise of 'scientific inquiry,' when that inquiry has definite, cognizable, and not insubstantial commercial purposes" (Roche, 1984).

In response to the *Roche* decision, Congress passed the Drug Price Competition and Patent Term Restoration Act later that year (Public Law 98-427). The Act overruled *Roche v. Bolar* on the specific issue of drug testing for FDA approval. Thus, Congress decided that, as a matter of national priority, drug makers (primarily generic drug makers) are not liable for infringement if their activities are solely to develop information for regulatory approval, in this case FDA approval. The U.S. Supreme Court further interpreted the law to apply to the use of any product subject to premarket government approval covered by any Federal drug law, including medical devices (Eli Lilly and Co., 1990). This statutory exemption has been broadly construed. The Federal Circuit Court found that activities yielding data that had been used for fundraising, marketing, demonstrations, and FDA approval was noninfringing and fell within the scope of the exception (Teletronics Pacing Systems, 1992).

Would researchers be liable for infringement when conducting research on patented human DNA sequences, or would their activities fall within the scope of the experimental use exception? Research to elucidate the function of a sequence, if carried out by academic scientists with no commercial goal in mind, might qualify under the experimental use exemption, as might research to confirm the accuracy of the patented sequences, or even research aimed at producing the protein products for which the sequence codes, as long as such research were not tied to any commercial goals. Still, much biomedical research, especially genetic research has commercial potential. As chapter 5 elaborates, universities and other nonprofit research institutions actively pursue patents on the fruits of their research efforts and seek licenses or use other mechanisms to commercialize them. Likewise, industrial scientists conduct basic research, but it is often specifically aimed at future commercial products, even if at the time of their research they have no idea if a commercial product will emerge.

For example, once a DNA sequence has been identified, researchers or their institutions often file a patent application with claims to the protein product even if it is remotely useful. Consequently, the narrow scope of the experimental use exception might not shelter much human genome research activity, even when conducted in universities and nonprofit institutions. Nor does the experimental use exception protect universities from licensing restrictions.

Distilling the case law on experimental use suggests that research with any commercial dimension, even only potentially, is not free of infringement risk, regardless of whether the research is to develop new, noninfringing alternatives (called “engineering around a patent”). In light of this, there are many who feel that the cost of litigation and the uncertainty it creates for research and commercialization plans militate in favor of either securing a license for the invention or avoid using the patented invention altogether. Sometimes, discussions with the patent owner are successful in ensuring against liability, especially for nonprofits. On the other hand, a century of jurisprudence surrounding the experimental use exception has not resulted in a decision where research into the nature of a patent invention resulted in infringement (Insert box 3-E). Many companies do not sue

university researchers in part because they cannot recover significant monetary damages and in part because they want more research done to improve the basic patented invention.

In practical terms, the likelihood that universities and small biotechnology companies would be sued for infringement depends on whether their research creates a significant commercial threat to the patent holder, the ease of detection and proof of infringement, and the vulnerability of the patent to a validity challenge. Rarely has university research been held to be an infringement. Furthermore, it is important to distinguish between university research aimed at analyzing or studying a patented invention for further development (a goal consistent with the patent system), from the use of patented tools by researchers in clinical studies. Conducting research with patented tools is an infringement; conducting research on a patented tool, such as a DNA probe, is favored and promotes innovation.

Dedicating the Invention to the Public

Obtaining a patent does not require the patent holder to practice, promote, or commercialize the invention. The patent holder could obtain exclusive rights and then not develop, sell, or use the invention. Most patent applicants, however, intend to use their discoveries in the commercial context in order to recoup the investments of time and money.

If an inventor wants to allow free public access to the invention, the inventor can simply publish the invention and not obtain a patent (box 3-F). Alternatively, patent holders could obtain patent rights and then dedicate the invention to the public. Few do. With such an approach, the patent holder foregoes enforcement of the patent rights by choosing not to pursue infringement actions that prevent third parties from using the invention. Overall, the government is one of few patent holders that has willingly dedicated its patents to the public, for example NIH stated that it would dedicate the sequencing methods in the EST patent application to the public. Cetus dedicated its invention of recombinant plasmids for producing human insulin to the public (H245, 1987). Theoretically, this ensures that the discovery will be widely available at reduced cost, since the

government, in choosing not to enforce its patent rights, would not charge a royalty or licensing fee. It also could prevent competing discoverers from blocking off areas of investigation. Due to technology transfer goals, the U.S. government has not dedicated many patents to the public. Dedication to the public of initial sequences or other inventions may not necessarily result in access to improvements on the early invention. Subsequent inventions may be patented and therefore, dedication of the initial invention to the public may be only a temporary spur to further scientific advances in the field, and may impede the objective of the dedication of the original discovery.

The economic rationale for governmental public dedication of patent rights is that governments spend tax revenues to subsidize research that leads to inventions, and so taxpayers should not be required to pay twice for an invention--once for the research and once for the patented product produced by the research. On the other hand, commercial development of government inventions might languish unless industry is assured an exclusive property position to support additional investment necessary for product development.

PATENTING HUMAN DNA SEQUENCES

How have the requirements for patentability applied to applications involving human DNA sequences? The fact that PTO even considers patent applications involving human DNA sequences arises, in part, from an historical U.S. Supreme Court decision. In *Diamond v. Chakrabarty*, the court considered whether a genetically modified bacterium was patentable and, in a 5-4 decision, declared that “anything under the sun that is made by man” is patentable subject matter. Thus, the court paved the way for a variety of human made living organisms, including genetically engineered mice, to be patented, as well as other genetic inventions.

Patents Granted on Human DNA Sequences

Patents on biotechnological developments date from the early days of the United States patent system. Louis Pasteur received a patent for a process of fermenting beer in 1873. Acetic acid

fermentation and other food patents date from the early 1800s, while therapeutic patents in biotechnology were issued as early as 1895. The first patent for isolating nucleic acid was issued in 1945, and the first patent for preparing ribonucleic acid by a fermentation process was issued in 1966. Still, to what extent has PTO issued patents on human DNA sequences? Have the types of patents involving human DNA sequences that PTO has granted evolved over time?

As part of this assessment, OTA analyzed all human DNA sequence patents granted by PTO from 1980 through December 31, 1993. (OTA chose 1980 because PTO granted the Cohen-Boyer patent for the underlying technique to produce recombinant DNA molecules that year.) OTA's analysis revealed that PTO granted 1,289 human DNA sequence patents claiming multiple DNA sequences during this time period. The number, breadth, and scope of U.S. patents that involve human DNA sequences suggest the importance of patents to commercial biotechnology. For 1,029 of these patents, the inventors were U.S. citizens. Of the remaining patents, 100 inventors were Japanese, 155 were European, and in 10 the inventor was non-U.S., non-Japanese or European. For some patents, both U.S. and non-U.S. inventors were named.

Of the 1,289 human DNA sequence patents, 534 were assigned to a U.S. company, 49 were assigned to the U.S. government, 444 were assigned to a university or nonprofit institution, and 252 were assigned to a non-U.S. entity. In all, the U.S. government was involved in providing at least some funds for research leading to at least 239 patents.

Not surprisingly, OTA found the scope of the claims for human DNA sequence patents narrowed significantly during the time period reviewed. Moreover, patents became lengthier, with more detailed information about sequences and claims, over time. 638 inventions claimed a diagnostic or treatment, 502 inventions claimed a research tool, 154 inventions claimed a probe, 472 inventions claimed a human protein, 63 inventions claimed a vaccine, 858 inventions claimed a process, and 913 inventions claimed a product. 224 patents claimed a full gene, and 825 patents claimed a gene fragment. The average pendency of each patent application from date of filing to date of issue was 1,080 days. There were no statistically significant differences between the pendency for applications

claiming full gene claims and those claiming gene fragments.

To what extent will patents on human DNA sequences, particularly sequences identified through federally funded research, assist or retard commercialization? (*Further analysis to come.*)

Moratorium on Biotechnology Patents

Despite the fact that PTO has granted patents on human DNA, controversies over patenting nonhuman living organisms and patenting human DNA sequences has led to fears over patenting human organs and, ultimately, of humans. To quell such concerns, proposals have been made to impose a moratorium on all biotechnology-related patents, particularly those involving human or animal genetic material, until the ethical qualms about the scope of ownership rights are resolved (Kimbrell, 1992).

Evaluating the impact of a moratorium one must consider the potential harms such an action will prevent against potential harms it will cause. On the one hand, proponents of a moratorium suggest that the principal harm induced by human DNA sequence patents is of an ethical nature. Another concern is that the threat of blocking patents might impede research. Chapter 4 explores the ethical considerations surrounding patenting human DNA sequences.

Some argue that a moratorium on human DNA patents may have disastrous implications for further scientific developments, notwithstanding the views of some academic scientists. Academic science is increasingly funded by private interests. This immense research expenditure which supports biotechnology inventions and product development will not occur without the promise of a financial return. To be sure, individual companies and their shareholders, profit from patented inventions, but the public also benefits because it can use new technologies and developments. A moratorium jeopardizes the private investment component.

Another consequence of a moratorium would be an increased level of secrecy and restricted

flow of information. This would actually harm the research communities, as the absence of patent protection would cause commercially-sponsored research entities to restrict dissemination of any character of their research. Increased reliance on trade secrecy is the most logical result of decreased availability of patent protection. In the eyes of researchers, patents delay access to information; in the eyes of lawyers, prohibiting patents would deny access to information.

As OTA's survey of researchers demonstrates (ch. 5), few academic molecular biologists state that the potential patentability of their research drives their research agendas. Moreover, few researchers reported that the NIH patent applications, even if granted, would affect their research or that of their colleagues. It appears likely that a moratorium on human DNA sequence patents would not affect academic molecular biology researchers' agendas.

Still, as OTA's analysis demonstrates, human DNA sequence patents have issued for over a decade. Imposing a moratorium on biotechnology patents, then, stands to potentially harm some stakeholder. In fact, a moratorium would have the greatest and most direct impact on the pharmaceutical industry, especially the commercial biotechnology sector. In turn, ripple effects would emanate to the financial sectors that support biotechnology.

As mentioned in chapter 2, the attraction of human genome research stems from the expectation that new diagnostics and therapies will soon follow. Today, the U.S. based pharmaceutical industry is a leader in the discovery and development of new drugs, particularly important new drugs with global markets. Since 1961, the U.S.-based industry has introduced about 25 percent of every new compound to the world market (Burstall, 1985; Redwood, 1988; OTA 1993) and is, so far, the unchallenged leader in biotechnology-based drugs and vaccines. Dedicated biotechnology companies are almost exclusively a U.S. phenomenon; no other country has a remotely comparable number (OTA, 1991). The first 15 biotechnology-based drugs and vaccines approved by the Food and Drug Administration were developed by U.S.-based firms (OTA, 1991).

A moratorium also would negatively affect U.S. competitiveness, since pharmaceutical and biotechnology companies maintain their exclusive market positions by exercising their intellectual

property rights. Further, intellectual property protection historically has been a problem for the pharmaceutical industry: Many countries, particularly newly industrialized nations, do not allow patent protection for pharmaceuticals (OTA, 1991). Still, experts generally regard elements of U.S. patent law as an important factor contributing to the success of U.S. commercial biotechnology. And while a moratorium would affect both U.S. and non-U. S. entities, U.S. companies, universities, scientists, and investors would bear by far the greatest burden. A moratorium would impede the commercial incentives to pursue research and development of new diagnostics and biologics. For human DNA sequence patents, for example, nearly 80 percent of those issued to date in the United States were assigned to a U.S. company, the U.S. government, or a U.S. university or nonprofit research institution.

Ultimately, of course, the public--as consumers of biotechnology products in the form of medical therapies or improved agricultural products--would be harmed if companies were to cease or curtail research in development in response to an inability to obtain patents.

LICENSING

An inventor might not have the desire or capability to commercialize a patented invention, and so might grant a license to a third party in order to commercialize it. An inventor also may sell, or assign patent rights to another individual or institution. When licensing is the selected approach the nature of licensing agreements has implications for future research agendas, commercial incentives, profits derived from products, and public interest.

Inventors use patent rights to choose whether and how to license an invention, concomitantly controlling to some extent commercialization efforts. Whether and how a patented invention is licensed and commercialized is critical to its access by a wider community and realization of a greater social benefit. Restrictions on access to patented discoveries can impede complete development of products. If, for example, a single entity were to hold patents on major portions of the human

genome, the licensing strategy would be critical to those wanting to develop the discoveries into useful products. The licensing strategy determines when, how, and at what price a third party will have access to a patented invention.

A patent holder has several options for providing access to a patented invention. An invention could be dedicated to the public, or an inventor may elect not to enforce the patent rights and allow others to freely use the invention without charging a fee or royalty. More likely, the patent holder will license the invention on an exclusive or nonexclusive basis, sell, or assign the patent rights. An exclusive license means that one entity has been given all rights held by the patent owner. The patent owner can exclusively license each claim in an invention to a different entity. A nonexclusive license means that the patent owner has licensed the same invention to several discrete entities. The character of the license arrangement will vary with respect to its value to the licensee, as well as how the licensee will be able to proceed in commercializing the invention. In return for gaining access to the patented invention, a licensee may pay a royalty or licensing fee to the patent holder. The various fees may be structured so that the licensee pays a lump sum based on the expected income stream of the commercial product, pays a fixed fee, or pays a percentage of income received by the licensee over the life of the license.

A patent holder may place restrictions or conditions in the licensing agreement. For example, the patent holder may require that the licensee make a diligent effort to develop the patented idea, or restrict the quantity or timing of production. Inventors with restrictive licensing terms, however, may face difficulties finding a licensing partner.

The larger issue related to exclusive licensing is that it reserves the patent right for fewer entities. Things that are costly to develop but are easily reproduced are likely to be exclusively licensed. This is because an exclusive license provides the safety of restricted market access for the patented technology. In contrast, processes that have broad market potential are more likely to be licensed on a nonexclusive basis because it will generate a broader revenue stream than through

exclusive licensing.

License fees and license contract negotiations place a burden on laboratories and the public. American College of Medical Genetics (ACMG) recent survey of private and academic clinical molecular genetics laboratories found that 52% of responding laboratories pay royalties on at least one license. Currently, 11% of the laboratories pay royalties on more than one license. Another 30% are negotiating license contracts. Approximately 85% of the laboratories pay royalties for access to PCR technology. The royalty fees are based on a fixed percentage of reimbursements or revenues on tests using the product. These percentages range from 9-12% of net revenues for most laboratories. 26% of the laboratories reported that they currently pay royalties or are negotiating royalty agreement for tests using cloned genes. Tests for many disease require multiple test systems. For example, fragile X diagnosis uses Southern blot assays and PCR amplification. The laboratories pay several fixed percentages on the total test cost. More complex tests, such as Duchenne muscular dystrophy could include 4 to 5 components, resulting in total royalty fees being 50-60% of net revenue. Meeting the costs of licensing can drive up the price of a final product, with the fear that the test becomes unaffordable, or the access severely limited.

Nonexclusive Licensing

A nonexclusive license is an agreement between the patent holder and several other parties. It permits more than one person the right to use the invention. In 1980 Stanford University and the University of California (UC) were awarded the Cohen-Boyer patent on the basic technique of gene splicing. Although a fundamental technique was patented, Stanford's and UC's realistic licensing policy ensured that the technique was widely available at minimal cost to all who asked. The licensing pitched the required royalty at a level that was not a deterrent to researchers, but also provided income to the Universities. This is an example in which a patent was not an impediment to researchers or industry, and still provided income to the Universities.

Exclusive Licensing

Under an exclusive license, the patent holder grants access to only one or a limited number of individuals or institutions, thus extending the monopolistic position held by the patent holder to the licensees. In general, licensees are unwilling to invest time, resources, money, and lost opportunity costs to develop an invention into a marketable product, unless they are guaranteed an exclusive market position. An example of an exclusive license is that for the polymerase chain reaction (PCR). PCR is a method of amplifying or copying DNA many times to produce a sufficient quantity of DNA for further analysis. Company, university, forensic and hospital laboratories are but a few of the many entities using PCR. In some instances, institutions purchase PCR test kits, which include a licensing fee within the purchase price. Hoffmann-La Roche exclusively licensed PCR to Kodak, Roche, and Perkin-Elmer--that in turn made sublicenses available on a nonexclusive basis for people wanting to use PCR (box 3-G).

Another example of exclusive licensing is the arrangement for transgenic animals, particularly the Harvard Oncomouse. Although Harvard granted an exclusive license to E.I. duPont de Nemours & Co. (duPont), duPont in turn granted nonexclusive sublicenses to purchasers of the oncomouse. However, while the oncomouse was made available to researchers on a nonexclusive basis, there were other licensing restrictions, namely breeding restrictions and pass-through rights (box 3-H).

Early patents may have several unintended applications which the exclusive licensee may not be interested in pursuing. Unless the license agreement was appropriately written, it may become difficult for the academic researcher to obtain funding from other source to develop these later discovered applications. Thus, the license mechanism and not the patent itself, may impede improvements on the early invention.

Cross Licensing

Cross licensing of inventions usually occurs when two or more parties have patented inventions needed by the other. The parties license their inventions to each other, or cross license the inventions. The obvious example of the need to cross license arises with blocking patents. In this case, the dominant patent holder will need a license from the subservient patent holder if he or she wishes to use the improvement. The dominant patent holder has an incentive to license the improvement either because (theoretically, at least) the improvement is a more efficient way of producing the product or it can profit from the expanded market. The subservient patent holder, in order to utilize the improvement, must obtain a license from the dominant patent holder in order to practice the improvement. Without a license for the initial invention, the second patent holder cannot practice the improvement. Thus, the two parties are both served by licensing their inventions to each other.

Compulsory Licensing

When patents are implicated as part of a monopoly pricing scheme (usually thought of as prices in excess of world prices for close substitutes), the possibility of government invoking compulsory licenses as a control mechanism exists. U.S. business strongly opposes compulsory licensing. Moreover, the effectiveness of compulsory licensing is not well understood (Lesser, 1991). In the United States, the patent grants exclusive rights, including the right to set prices at any level. In exchange, the monopoly term is limited, and following the patent's expiration other competitors may enter the market with prices regulated through market forces. The U.S. allows compulsory licensing only in cases of national security and national need (for plant breeders' rights under specific statutory grants of authority, namely the Union for the Protection of Varieties, and Plant Variety Protection Act).

World Intellectual Property Organization (WIPO) Model Law for Developing Countries on Inventions establishes three grounds on which compulsory licensing can be granted: (1) for nonworking or insufficient working (for national production or use); (2) to avoid infringement where

the existence of an earlier patent prevents the exploitation of an important technical advance covered by a later patent; and (3) to protect public interest, in particular as relates to national security, public health, or significant economic activity. A more recent international instrument governing compulsory licensing is the TRIPS Agreement of the Uruguay Round, which will come into force next year.

Clearly, the requirement that a patent holder license an invention dilutes the patent right, since it mitigates the patent holder's ability to regulate the exploitation of the invention. On the other hand, every country has national interests that take precedence over individual property rights. The key is balancing governmental need with individual rights.

A compulsory licensing regulatory scheme could be an alternative to a broad prohibition on patenting classes of products. In the biotechnology arena, for example, compulsory licensing could represent one method to obviate the need for a moratorium on all human gene patents through licensing conditions which address social and ethical concerns. For example, the social costs of exclusive rights, such as sitting on patents to stifle new developments that threaten markets for existing products, are addressed by allowing multiple groups to further explore and develop patented DNA sequence data. Compulsory licensing is not free access--a fee could be charged in connection with granting the license. Just the existence of a compulsory license regulation, however, could serve as a deterrent to social costs of exclusive rights by allowing multiple groups to further explore and develop patented DNA sequence data. This view assumes that sequence data would be available without the incentive provided by exclusive intellectual property rights. On the other hand, some view compulsory licensing as ill-suited to address perceived social costs of patents, since it conflicts with the concept of exclusive rights granted by a patent. They argue that compulsory licenses would restrict the manner in which patent rights are exercised, changing the location of research and manufacturing to outside the U.S.

Compulsory licenses could be granted in the case of dependent patents--i.e., a compulsory license could be granted to allow a dependent patent holder to exploit an invention without infringing the earlier patent. Additionally, a compulsory license also could be granted on public interest

grounds--health, safety, nutrition, or national security.

ALTERNATIVES TO PATENTS

Intellectual property protection is broader than patent rights. If a creation is not patentable, inventors could secure copyright protection. Alternatively, inventors can keep their discoveries secret, through trade secret protection. This section reviews copyright and trade secret protection.

Copyright

Like patents, copyrights on “writings” find their roots in the Constitution. Historically, the term “writings” has been broadly interpreted. The copyright statute (17 U.S.C. § 102 (a)) defines a writing as that which is “fixed in any tangible medium of expression, now known or later developed, from which they can be perceived, reproduced, or otherwise communicated, either directly or with the aid of a machine or device.” Copyright expressly protects eight categories of works: literary; musical; dramatic; pantomimes and choreographic; pictorial; graphic and sculptural; motion pictures and other audiovisual works; sound recordings; and computer programs.

A copyright does not protect an idea, but rather the expression of the idea. Thus, a copyright does not protect against independent development, only against copying. Copyrights do not extend to any procedure, process, system, method of operation, concept, principle, or discovery, regardless of the form in which it is described, explained, illustrated, or embodied (17 U.S.C. § 102 (b)).

Copyrights protect the form of expression rather than the subject matter of the writing. Copyright protection, for example, would extend to a writing that describes a machine. Such protection would prevent others from copying that description; it would not prevent others from writing a description of their own or from making or using the machine itself

Initially, commentators suggested that DNA sequences were copyrightable as expressed information (Kayton, 1982). They argued that DNA is like computer software programs, since both

are sets of instructions (Kayton, 1982). The U.S. Copyright Office, however, has unofficially stated that DNA molecules and gene sequences do not constitute copyrightable subject matter, a position that would likely extend to engineered proteins (Bahn, 1987). Even if such information were copyrightable, the protection afforded arguably would be inferior to that provided by a patent, since under copyright law, the copyright holder could not prevent others from independently making or sequencing the same information.

Clearly copyrights afforded weaker protection than patent rights, and early on scientists sought and received patent protection for mammalian (including human) DNA sequences and proteins. In fact, between 1980 and 1993, PTO has granted almost 1300 patents involving human DNA.

Although the copyright approach was discarded initially in favor of the greater intellectual property protection of patents, copyright again has been raised as an appropriate way to protect EST sequences if they are not patentable. Such an approach avoids the utility, and nonobvious issues and could allow others, namely researchers, access to the sequence information without first obtaining a license. One unanswered question for copyright protection of ESTs is, however, who is the creator? The researcher who sequences the information arguably is not the creator of the sequence; he or she merely unlocks the code.

Copyright law has a provision that in some ways applies the experimental use concept to books, movies, software, and other copyrightable works. The statutorily defined “fair use” defense to copyright infringement states in part that “the fair use of a copyrighted work . . . for purposes such as . . . scholarship, or research, is not an infringement of copyright” (17 U.S.C. § 107 (1982)). Despite the seeming breadth of the phrase, fair use is not universally applied to educational and research-related activities. Indeed, recent cases have increasingly emphasized whether the infringing work cuts into the market for the copyrighted work. This consideration dominates even where the work is sold primarily for an educational market (Leval, 1990).

Still, two recent copyright cases suggest an expansion of fair use under circumstances similar

to those that researchers could encounter with patented DNA sequences (Atari, 1992; Sega Enterprises, 1992). In these cases, copyrighted elements of video game interface software--the software that allows a game cartridge to run on a particular manufacturer's game hardware--were copied by competitors wanting to sell video games capable of running on that hardware. Courts in both cases extended the fair use defense to excuse this activity from infringement liability.

These cases resemble a scenario much discussed by researchers concerned with EST patents. When a genetic researcher uses a patented EST (or larger fragment that includes it) to identify a larger sequence, or even clones the gene (which of necessity includes the EST), he or she is in a similar position as the competitors who wanted to sell video games that were compatible with the hardware sold by the owners of copyrights for the hardware/software interface code. The researcher may infringe this patent to do the work, even though that work is removed from the domain of the patent. For instance, the inventor could have identified the gene associated with the EST, and perhaps cloned it, with an eye toward using its expression product therapeutically. The video game competitors, by analogy, were not interested in selling competing versions of the video game interface code; they were just using it to achieve their quite different (and perhaps more difficult and socially valuable) goal of selling video games they had developed themselves. Like the video game sellers, the genetic researcher must infringe a property right on the way to a goal perhaps unrelated to the subject matter of the property right. Nevertheless, patent law's experimental use exception, as described earlier, does not have nearly the same breadth as the copyright fair use doctrine.

Trade Secrets

Trade secret protection extends to information used in one's trade or business that is maintained as secret by its owner and provides a competitive business advantage over those not having the information. A plan, process, tool, mechanism, chemical compound, customer list, or formula are all examples of information that can be maintained as trade secrets. An inventor must take affirmative steps, especially if it is an employer, to keep information secret--e.g., by limiting

access to the secret information or by requiring people with access to sign confidentiality agreements. Universities point out that a trade secret approach to DNA sequence information generated by academics conflicts with the university mission to disseminate knowledge they generate.

Unlike patents, which are governed exclusively by Federal law, state law governs trade secrets. Stealing a trade secret is a tort and action lies against the thief for misappropriation. It is not misappropriation if one obtained trade secret information and did not know that such information was a trade secret. The trade secret owner might have a cause of action for wrongful disclosure, however, against the disclosing party. Trade secret law in the United States has been fashioned to promote two beneficial ends. It encourages commercial morality and fair dealing, and it encourages research and innovation. Unlike patent law, however, it does not promote disclosure to the public.

Trade secret rights require that a trade secret be disclosed in confidence only to those having a reasonable need to know (e.g., employees). These rights require that measures be taken to prevent disclosure of the trade secret to the public or to competitors. Companies generally identify what information constitutes trade secrets so that they will have enforceable rights. A person entering into a confidential relationship with a trade secret holder, therefore, must know what is considered to be the trade secret. If someone discloses a trade secret in violation of a confidential agreement, rights are lost forever. Unlike a patentee, a trade secret holder has no recourse against a later independent developer, or even one who discerns the secret by analysis of the products placed on the open market by the owner. Only abuse of a confidential relationship creates liability.

Attempts to keep DNA sequences as trade secret information probably would not be effective for three primary reasons. First, much of DNA sequence information is generated by universities where trade secrets conflict with the institutions' mission to share information. Second, DNA sequence information is relatively easy to obtain, so a researcher interested in a particular chromosome can identify the sequence of interest. There are DNA libraries with sequence information available and automated sequencing processes to facilitate researchers access to information. Third, if the DNA sequence is to be commercialized as a therapeutic, there is an average

delay of 10 years for a sequence and its protein products to be available as a therapeutic. As part of this 10 year development, the product is tested in public clinical trials, thus making it more difficult to keep the DNA sequence secret. Although FDA applications and investigational new drug proposals are confidential, grant applications that might disclose DNA sequence information, once funded, are public documents. Since no income accrues during clinical trials, companies without secure financial reserves might need to use DNA sequence information to raise capital. The relative ease of identifying a DNA sequence and the time lag for product development may prove that the trade secret approach to protect DNA sequence information is undesirable.

SOCIAL ISSUES

Apart from the legal patentability requirements, are there reasons an invention might not be patentable? In a few instances, courts have found that inventions are not patentable because they are immoral. Additionally, the U.S. Constitution prohibits the ownership of humans. Thus, intellectual property rights in human DNA sequences should be examined in light of possible moral and constitutional concerns.

Prohibitions on Patenting Illegal or Immoral Inventions

Certain inventions are not patentable because they are “injurious to the morals, health or good order of society” (Brenner, 1966). Merely because an invention carries the possibility of illegal use is not grounds for denying a patent. If the only use for an invention, however, is illegal, the invention will not meet the utility requirement (35 U.S.C. 5 101). At one time, gambling machines were not patentable because they promoted gambling, which at the time was illegal because it was considered to be immoral (Puller, 1903; Koppe, 1929).

The vast majority of patent lawyers argue that using patent law to restrict research or development in a particularly troublesome moral or ethical area is inappropriate. Patents grant the right to exclude others from making, using, or selling a patent product--they do not regulate the use or

development of an invention. These experts agree that if one has concerns about the moral ramifications of the Human Genome Project, then regulating the use of, or access to the discoveries should be explored, but intellectual property protection of discoveries should be unfettered--especially since regulatory issues are beyond the scope of U.S. patent law and PTO jurisdiction.

Thirteenth Amendment: Slavery and Patenting

Until 1980, PTO did not grant patents on living organisms, whether they were naturally occurring or genetically altered through human intervention. Although patent applications were rejected if directed to living organisms per se, patent protection was granted for many compositions containing living things, such as sterility test devices containing living microbial spores, food yeast compositions, vaccines containing attenuated bacteria, and various dairy products. In 1980, the U.S. Supreme Court ruled that live, human-made microorganisms qualified as patentable subject matter under the “composition of matter” definition (Diamond, 1980). In April 1987, the Board of Patent Appeals and Interferences ruled that polyploid oysters were patentable subject matter, thereby allowing patenting of nonnaturally occurring, nonhuman, multicellular living organisms.

In 1988, PTO granted the first animal patent to Harvard for a transgenic mouse (U.S. 4,736,866). The patent included a broad claim, covering all transgenic, nonhuman oncomammals and sparked great debate over issues concerning patenting animals, especially ethical considerations. Of particular concern was whether humans could be patented.

In April 1987, PTO announced that a “claim directed to or including within its scope a human being will not be considered to be patentable subject matter under 35 U.S.C. § 101,” because granting a limited but exclusive property right in a human would be unconstitutional (OTA, 1989). No specific section of the Constitution was referred to in PTO’s announcement, although there was speculation that the 13th and 14th Amendments served as the basis for the decision.

Thus, an additional legal issue about patenting human DNA is whether it violates the 13th

Amendment to the U.S. Constitution. The 13th Amendment of the U.S. Constitution states “Neither slavery nor involuntary servitude, except as a punishment for crime whereof the party shall have been duly convicted, shall exist within the United States, or any place subject to their jurisdiction.”

Involuntary servitude encompasses “the control of labor and services of one man for the benefit of another, and the absence of a legal right to the disposal of his own person, property and services” (Plessy, 1896); “a condition of enforced compulsory service of one to another” (Hodges, 1906); “that control by which the personal service of one man is disposed of or coerced for another’s benefit which is the essence of involuntary servitude” (Bailey, 1911).

The 13th Amendment was enacted to eliminate slavery, but since enactment, the 13th Amendment has been used as the basis for a number of legal claims, primarily involving forced labor of prisoners, government collection of income in bankruptcy cases, and class discrimination. The amendment also has been applied to the abortion issue and cases involving school children (Arnold,

Property rights and individual rights unite at the level of DNA. Many discussions on the constitutionality of granting patent rights on humans assume that patent protection will be sought for a transgenic human--not for a gene therapy patient, but a human with specific genetic alterations designed for a specific job. Or they assume an animal-human hybrid, such as pigs with human immune systems, to be used to harvest organs for transplantation into humans (Rivard, 1992; Note, 1989). Patentable claims would not be directed toward covering human body parts per se, but a composition in which an inventor has intervened, in accordance with the holding of Diamond v. Chakrabarty. With respect to 13th Amendment concerns, however, one main component of involuntary servitude is that it is, in fact, strictly involuntary. It would be difficult to imagine that undergoing gene therapy could ever be considered strictly involuntary because of informed consent requirements.

Owning the patent on a DNA sequence to be used in gene therapy is not equivalent to owning the actual DNA sequence. A patent grants the patentee the right to exclude others from making, selling, or using the patented material, but it does not grant the patentee possessory rights in every one

of the patented items. Patent claims to genome inventions involve ex vivo purified version of a DNA sequence or protein. This limitation distinguishes the claims to the invention from the natural product; the production or use of the natural product cannot be infringement. Thus, one does not infringe the claims in biotechnology patents simply by allowing bodily function; any claim that covered this activity would lack novelty.

A gene therapy recipient would not be subjugated, because the patentee for the gene would not own the part of the recipient containing the patented product. The insertion of a patented DNA sequence by the patentee into a patient exhausts the patentee's rights in the exclusive use of the sequence, regardless of whether money is paid. Hence, a person cannot be a walking infringement merely because the DNA sequence is within his or her body or because the protein is produced as part of a body function. Gene therapy can also be seen as a drug therapy. The gene therapy patient gets the gene by purchase or other agreement from the patent holder or licensee, and has all rights to use the product. This is just as if someone took a medication supplied by a pharmaceutical company. What distinguishes genes in treatment from other medications is that genes can make products in the body. The patient does not infringe the patent because the patent is to the "purified" product, not the diluted form in the body, and because the patient is not producing the product for sale. For patent rights to matter in vivo, they would have to constrain reproduction, along the lines of transgenic animal restrictions. To the extent that U.S. Supreme Court decisions maintain an individual's right to privacy to make reproductive decisions, the Constitution protects citizens from such restrictions.

International Approaches to Patent Prohibitions

In 1977, European nations centralized and standardized patent law and procedure through the European Patent Convention (EPC). To date, 17 countries adhere to the agreement: Austria, Belgium, France, Denmark, Germany, United Kingdom, Greece, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, The Netherlands, Portugal, Spain, Sweden, and Switzerland. Finland is expected to join in the near future. As of March 1, 1994 European Patents can be registered in

Slovenia.

Because the patchwork of traditional national patent systems in Europe was recognized as creating a potential conflict with the need for free trade, EPC established the so-called “European Patent,” which has the same effect as a national patent in those member countries designated in the European patent application. The rights in each designated state that result from a European patent are independent of those in other designated states. The rights are obtained by filing one application with the European Patent Office (EPO) in Munich. Once granted, the patent matures into a bundle of individual patents--one in each member country. A consequence is for each member country was to adopt, in its national law, the same substantive and procedural law of patents established by the EPC agreement.

EPC streamlines procedural requirements for applicants seeking a European patent. It avoids duplicate filing, searching, and examination costs, and economizes the use of professional time, both on the part of the applicant’s domestic patent representative and representatives in countries where protection is sought (Bent, 1987).

EPC patentability requirements and U.S. patent requirements differ in several key features. The EPC has three elements of patentability: novelty, inventive step, and industrial application. Thus, to meet the latter requirement, an EPC patent applicant must specify the potential application of the invention in the filing. Also, under the EPC, discoveries are not considered inventions. A discovery is an act, procedure or circumstance by which one acquires knowledge of something unknown or not yet recognized. Thus, under the EPC, one could argue that ESTs are discoveries but not inventions because the DNA sequence information is decoded, but not invented or created. This is in contrast with current EPC consideration of cDNA and DNA sequences (box 3-I).

Another difference between the EPC and U.S. patent law is the prohibition against patenting inventions for which publications or production would violate public order or morality. The expression ‘public order’ is the technical translation; the concept is closer to public policy. Procedures

allow anyone who opposes the issuance of a patent to present arguments to EPO. In the past, industrial competitors have taken advantage of filing an opposition, but more recently, public groups have filed oppositions to transgenic plant and animal patents and human DNA patents on the grounds that such patents would violate morality. The response of EPO Opposition Divisions to some of the oppositions based on public order and morality is:

- A patent does not give a positive right to use the invention, but rather confers the right to exclude others from using the invention for a limited time period.
- Patent law is a means to promote research and technical advances, but patent law can not suppress or censor an interesting line of investigation or promise of revolutionary discovery. Technologies that pose a threat to humanity should be regulated outside of the framework of patent law.
- It is inappropriate for EPO to prescribe the conditions under which a patented invention may be practiced. New technologies present new risks, and the balancing of the negative risks and positive aspects of any given invention should determine whether a technology should be used. Weighing trade-offs is best done through legislative discussions.
- The public order and morality provision is interpreted to mean that to be excluded from patentability, the working of the invention must be immoral (e.g., a letter bomb). This is distinct from whether the commercialization of the patent, once granted, could be contrary to morality. For example, according to EPO, using and protecting by a patent DNA sequences to develop a pharmacological product, or somatic gene therapy would not be immoral, but using DNA sequences in germ line gene therapy for the purposes of a patent application could be immoral and thus a bar to patentability.

EPO does not deny patentability under the public order and morality article merely because an invention has a possible negative application in addition to positive ones (Gugerell, 1994). The Boards of Appeal at EPO may alter this position as hearings of the multiple oppositions against the Harvard Oncomouse patent continue.

Proponents of transgenic animal and human DNA patents suggest that public order and morality opposition merely provides a way for minority groups that were unsuccessful in legislative debates in a democratic process to assert their positions.

SPECIAL PATENT REGULATIONS

Historically, industries have been singled out for unique patent treatment. Patent law has been used to control innovation and development of atomic energy in the interest of national security. In one case, the airline industry, special treatment was given to pool, or share between companies, patents to promote the development of a new industry. Most recently, the computer industry was given special patent treatment for semiconductors. Evaluating these case histories gives policymakers insight as to whether special patent legislation is necessary for human DNA sequences and the biotechnology industry.

Atomic Energy

In the past, inventions related to atomic energy were subject to a broad experimental use exemption from infringement. The Atomic Energy Act of 1946 (Public Law 79-585) provided that “No patent hereafter granted shall confer any rights with respect to any invention or discovery to the extent that such invention or discovery is used in the conduct of research or development activities in the fields specified in [the Act].” Congress deleted this provision by outlawing the patenting of all atomic energy-related inventions in the Atomic Energy Act of 1954 (Public Law 703) which prohibits patents but requires payment of “just compensation.” Prohibiting patent rights in the area of atomic and nuclear inventions is based on national security interests.

Airline Industry

Some patent issues currently facing the biotechnology sector have been addressed previously in the context of other industries. In its nascency, during the 1910s, aircraft manufacturing shared numerous characteristics with today’s burgeoning biotechnologies. At one time, flying was an infant technology that captured the imaginations and attracted the expertise of the technical community. Its projects were costly gambles and its destructive capacity for war uses provided ethical dilemmas. Aircraft manufacturing vested in a select few control of skies that previously belonged to no one. As

now, patent policy also was controversial then.

The prominent feature of patent policy in the aircraft industry was its long-lived patent sharing or pooling agreement. The agreement was proposed in 1917, revised in 1928, challenged by the U.S. Department of Justice in 1972, and dismantled by consent decree in 1975 (Bittlingmayer, 1988). It originally was proposed to resolve a patent dispute between the Wright brothers and Curtiss Aircraft (Manufacturers Aircraft Ass'n, Inc., 1933). Government officials proposed a settlement agreement that established the Manufactures Aircraft Association (MAA) for airframe makers.

Under the agreement, member firms voluntarily shared their current and future airframe patents for a fixed royalty. Members paid a \$1,000 initiation fee and a fee of \$200 for each airplane built (Vaughan, 1956). The agreement covered only airframes, which required multiple patents to produce. The agreement provided for royalties to be paid for patents deemed “significant advances,” and an arbitration board determined the royalties without recourse to litigation. The “significant advance” provision eliminated manufacturers’ fears that their future advances would be bargained away by joining the agreement. The Curtiss-Wright dispute is a classic example of the licensure hold-out problem that can arise with blocking patents.

With respect to antitrust considerations, pooling or cross-licensing of patents is not per se illegal without accompanying restrictions on output or price (Vaughan, 1956). Repeated probes into MAA concluded the pace of the industry’s technology development was not slowed (Bittlingmayer, 1988). One reason was that the agreement shifted the loss of less innovation from aviation consumers to manufacturers. It allowed competition between the manufacturers on nonairframe technologies, price, and nontechnical items. Although, it pooling decreased the incentive to develop alternative technologies.

The MAA had several effects. It substantially lowered the transaction costs of licensing covered technologies, association members had access to unlimited use of one another’s patents without negotiating separate licensure agreements for each patent, and it eliminated the uncertainties

associated with litigation as an enforcement mechanism.

Semiconductor Industry

The semiconductor industry also benefited from special intellectual property legislation. Semiconductor chip masks are expensive to develop, design and prepare. However, like computer software, they are relatively simple and inexpensive to reproduce. The fundamental technology for manufacturing chips is well established, so it is difficult to meet novelty and nonobviousness patent requirements. At the same time, copyright protection was not sufficient since chip design is too functional (NRC, 1993). In 1984, Congress passed legislation--Semiconductor Chip Protection Act of 1984 (Public Law 98-620)--that combined copyright protection of reproduction, importation, and distribution rights with patent law rights of excluding others from making or selling chips. The basic features of the law include a narrow subject matter, broad exemption for reverse engineering, and a term of protection limited to 10 years. The law was custom-designed for the semiconductor chip industry, but Congress attempted to maintain the balance between providing incentives for innovators, and promoting dissemination and use of the invention.

Additionally, Congress codified an experimental use exception to infringement of patents and related rights. An exemption applies to the rights conferred on semiconductor chip mask works; it was apparently added to the law to balance encouraging new mask work production against radically disrupting existing industry practices. The exemption has never been litigated, as the entire law became moot due to technological and industry evolution (Rauch, 1993).

One weakness of the Semiconductor Chip Protection Act is that it does not provide international protection nor does it coordinate with existing patent or copyright treaties (Goldberg, 1993). A separate treaty would have to be negotiated, in this case without international consensus on what sort of protection is appropriate (Goldberg, 1993). Under the law, however, the Secretary of Commerce has authority to issue temporary orders that extend the benefits of the law to nationals of countries "making good faith efforts and reasonable progress" toward signing a treaty with the United

States, or enacting domestic legislation similar to the Act (Goldberg, 1993). However, this is a temporary measure, and does not encourage consensus or consistency at the international level. The most recent round of GATT negotiations included a semiconductor chip patent protection provision. The Treaty on Intellectual Property in Respect of Integrated Circuits, negotiated under the auspices of WIPO and adopted at Washington, DC on May 26, 1989, requires parties to the treaty to provide an effective form of protection for such products. Although the treaty has not entered into force, the substantive provisions of the treaty have been incorporated in the TRIPS Agreement under the GATT Uruguay Round.

In addition to the Semiconductor Chip Act, the Plant Variety Protection Act also codifies an experimental use exception (Plant Variety Protection Act of 1970 (PVPA) (7 U.S.C. sec. 2321-2583). No reported decisions turn on this provision, but it is part of a broad pattern of limitations on the rights conferred under the PVPA. Farmers can save seeds from patented plants under this Act, for instance, and reuse them without fear of infringement. Farmers are also permitted to sell some of those seeds (up to 49 percent of the total acreage without violating the farmer's resale limitation) in competition with the holders of the PVPA right. In general PVPA's research exemption reflects the long tradition of open access to plant varieties by plant breeders (Kloppenburg, 1987; OTA, 1989).

SUMMARY AND CONCLUSIONS

Human DNA is patentable if it meets the elements of patentability, namely utility, novelty, and nonobviousness. In fact, in the past fourteen years alone, PTO has granted patents on more than 1200 inventions involving human DNA sequences or nonhuman sequences with human application. Thus, any policy action taken with respect to biotechnology or DNA patents must first recognize that the existing system has been dealing with this controversy for some time. The time taken to obtain patent protection may delay disclosure of new discoveries for a period of time, however, the overriding objective of the patent system is to promote disclosure, since the discovery is made public. This stands in stark contrast to the alternative to patents which is trade secrecy. Many wonder how universities and government can promote the exchange of scientific ideas and biological materials

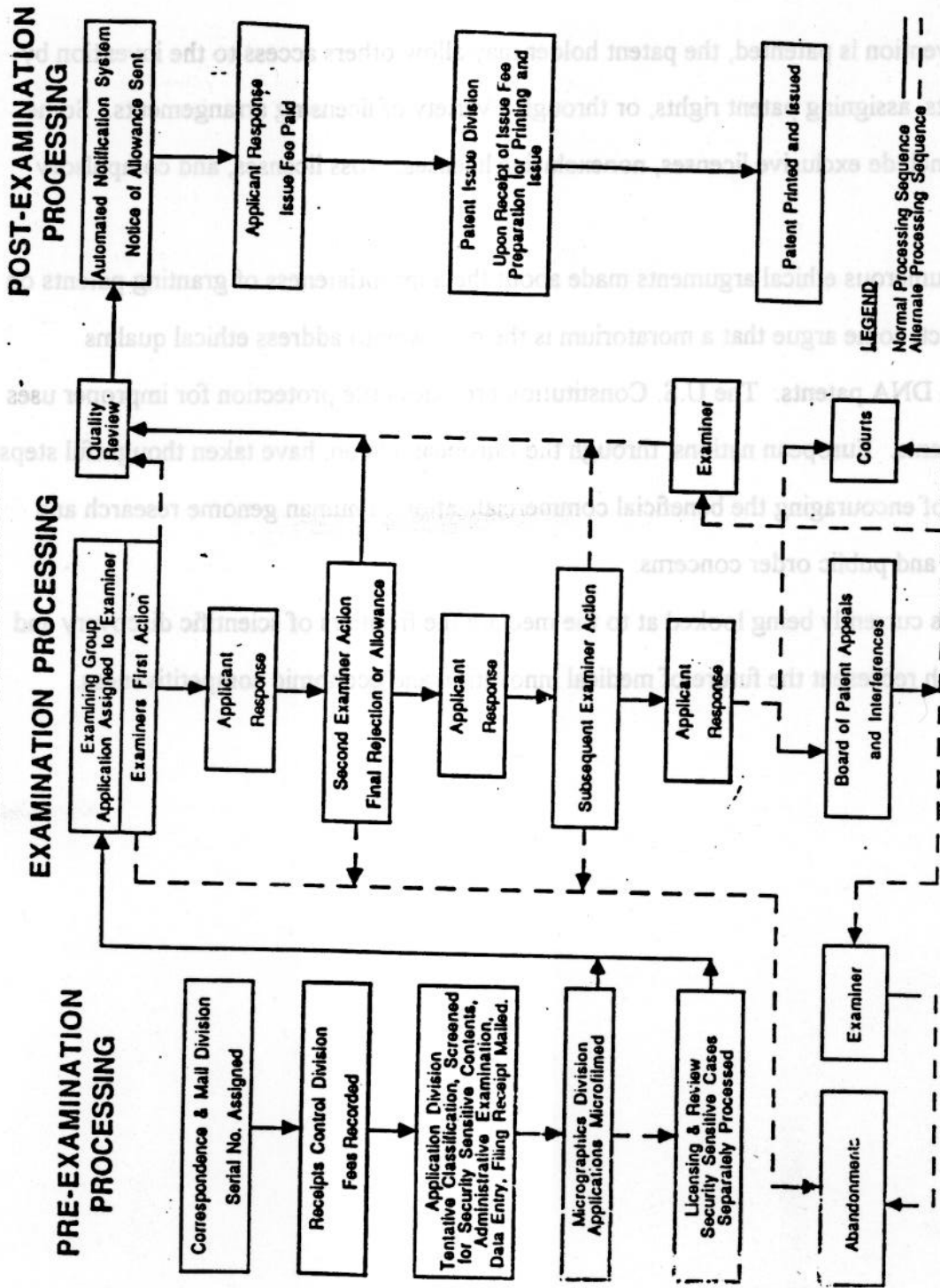
without compromising patent rights, for access to information and encouragement of investment to develop discoveries are driving forces behind polar views of the appropriateness of patenting human DNA.

Once an invention is patented, the patent holder may allow others access to the invention by selling patents rights, assigning patent rights, or through a variety of licensing arrangements. Some licensing schemes include exclusive licenses, nonexclusive licenses, cross licenses, and compulsory licenses.

There are numerous ethical arguments made about the appropriateness of granting patents on human DNA. In fact, some argue that a moratorium is the only way to address ethical qualms surrounding human DNA patents. The U.S. Constitution provides little protection for improper uses of human DNA patents. European nations, through the European Union, have taken thoughtful steps in looking at ways of encouraging the beneficial commercialization of human genome research and protecting morality and public order concerns.

Patent law is currently being looked at to the mediate the frontiers of scientific discovery and human inquiry which represent the future of medical innovation and economic competitiveness.

Box 3-A--U.S. Patent Process



PTO holds patent applications in confidence, and nondisclosure rules apply during the pendency of an application (35 U.S.C. 122). Only the application's owner may access the file; all others must obtain the owner's permission. Abandoned patent applications are similarly not generally available to the public, except under special circumstances, such as the NIH EST patent application, where NIH chose to waive its secrecy rights during the patent application process. Confidential patent information can be maintained as a trade secret. Once a patent issues, however, the information is publicly available so as to encourage further innovation. GRAPHIC SOURCE: U.S. Patent and Trademark Office, 1993.

Box 3-B -- *In re Durden* and Process Patents for Biotechnology

Process patents to derive sequences also might be deemed obvious under current law (*In re Durden*, 1985). Even if an invention uses novel and patentable starting material, the process may be deemed obvious and unpatentable. *Durden* involved a challenge to a denial of a patent for a process to make a novel chemical. The process to make the chemical, although similar to that of a previously issued patent, used a novel, though related, starting material and produced a novel, though related, end-product. Although PTO denied a patent for the process, it granted a patent for the novel starting material and the novel end-product. The court upheld PTO's decision, in *Durden*, that a chemical process, otherwise obvious, is not patentable--even if the starting material or the product is novel and nonobvious.

Although the technology in *Durden* did not involve molecular biology techniques, the *Durden* decision concerns applicants for biotechnology-related patents. PTO occasionally relies upon the decision to deny certain process patents (Wiseman, 1989). The Federal Circuit distinguished between *Durden* methods of making and methods of using (*In re Pleuddemann*, 1990).

PTO and opponents of the *Durden* decision argue that it is difficult for biotechnology firms to obtain process patents because recombinant DNA processes and automated gene sequencing processes are obvious (BNA, 1993).

While many support legislative efforts to overturn *Durden*, others argue that overruling the decision would lead to issuance of excessive numbers of process patents, thus diluting the obviousness requirement. Opponents of legislative action also argue that any legislation will result in uncertainty and additional patent infringement suits. There are two cases on appeal before the Federal Circuit which may resolve the conflict and obviate the need for a legislative solution.

SOURCE: Office of Technology Assessment, 1994.

Box 3-C -- Transgenic Cotton Patents

The agricultural sector of the biotechnology industry has been able to obtain patent with very broad claims. In 1992 Agracetus obtained a patent on all transgenic cotton, which claims rights to all genetically engineered products from the entire cotton species (Mestel, 1994). Agracetus originally filed for patent protection in 1986. Agracetus states that it intends to follow a policy of making available research licenses free of charge to all academic and government researchers, but has not yet made clear its licensing policy for commercial entities (Thayer, 1994). For example, Calgene has designed cotton that is genetically engineered to be herbicide resistant, but it is unclear if the Agracetus patent will be a barrier for market entry.

Some compare the Agracetus patent to the Cohen-Boyer patent, and point out that the licensing approach may set precedent for developments of new technologies for other crops. It could also indicate broad patent trends for other sectors of biotechnology, including human gene research.

SOURCE: Office of Technology Assessment, 1994.

Box 3-D -- Reverse Doctrine of Equivalents

The reverse doctrine of equivalents allows a defendant to avoid infringement if the defendant's device is "so far changed in principle from a patented article that it performs the same or similar function in a substantially different way" (Craver Tank, 1950). Even if a product is within the literal words of the claim, it is weighed against the equitable scope of the claims and may be found to be noninfringing.

The doctrine of equivalents helps the patentee by expanding the scope of claims beyond its literal boundaries (Merges, 1992). In a roughly symmetrical way, the reverse doctrine of equivalents excuses infringement under some circumstances. Courts have long recognized that, "[c]arried to an extreme, the doctrine of equivalents could undermine the entire patent system" (355 F.2d 400). Scope could be enlarged so far beyond the literal language of claims that patents would take on unlimited power. To check the potentially destructive impact of the reverse doctrine of equivalents and to preserve symmetry in the rules on infringement, the Supreme Court long ago ruled that:

a charge of infringement is sometimes made out, though the letter of the claims be avoided The converse is equally true. The patentee may bring the defendant within the letter of his claims, but if the latter has so far changed the principle of the device that the claims of the patent, literally construed, have ceased to represent his actual invention he is as little subject to be adjudged an infringer as one who has violated the letter of a statute has to be convicted, when he has done nothing in conflict with its spirit and intent (170 U.S. 537).

However, use of the reverse doctrine of equivalents is fairly rare. The reverse doctrine of equivalents, although frequently argued by infringers, has never been applied by the Federal Circuit Court (Erllich, 1991). It was mentioned by the court in one case, but was not relied upon in ultimate resolution of the case (Scripps, 1991).

SOURCE: Office of Technology Assessment, 1994.

Box 3-E -- Comparative Experimental Use Standards

Many countries have codified their judicially-created experimental use exception to infringement liability. Some European nations responded to the need to harmonize their patent laws, whereas Japan considered an experimental use statute to be in the public interest. U.S. legislation, extending the experimental use defense to the area of drug testing and approval activities, overruled the Federal Circuit Court's holding in *Roche* (Public Law 98-424).

Japanese patent law provides that the effects of the patent right shall not extend to the working of the patent right for the purpose of experiment or research. The term "experiment or research" is not limited to academic purposes, but includes industrial tests or research. In addition, this statute has been interpreted to permit a commercial enterprise to use a patented invention to create new technology. However, Japan does not extend the defense to regulatory testing of products, as this is considered a commercial use.

European Patent Convention provides that patent protection shall not extend to "acts done for experimental purposes relating to the subject-matter of the patented invention," the national patent laws of many member countries now reflect this language, including Germany, France and the United Kingdom; other Community member nations have such legislation pending. Certain nonmember countries, such as Sweden, have similar provisions in their national laws. Like Japanese law, these European laws generally permit testing to craft new products while excluding regulatory testing of products from the experimental use defense.

The United States is the only country that extends the experimental use exception to the limited area of drug testing and approval activities. The drug regulatory testing exemption, part of the Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-424), explicitly excludes regulatory testing of certain inventions from the scope of patent protection. This exemption from liability was the *quid pro quo* for the Act's extension of drug patent terms, which was designed to offset lengthy regulatory delays at the Food and Drug Administration. Since passage of the original

Act, Congress has twice expanded its scope. First, Congress extended coverage of the Act to include some veterinary drugs and biologicals in 1988; and second, in 1990, when the Supreme Court interpreted the statute to apply to medical devices as well as drugs (Eli Lilly & Co., 1990).

Because of the relative specificity of the U.S. exemption, it does little to answer the key questions on the general scope of the experimental use exception in the United States. For example, it does not address a case where a patented invention is used--perhaps only once--as a springboard to create a noninfringing alternative or improvement; as mentioned, Japan and Europe consider the use in the later example to be noninfringing. Of concern then, is a situation where the U.S. position differs from Japan and Europe. Research organizations and companies might shift their experimental laboratories to Europe or Asia to escape this barrier to conducting research with patented inventions. With respect to pending EST patent applications, researchers faced with reasonably broad patents might also be in this position, as they could find it necessary to infringe on some of the patent's claims to characterize, isolate, and clone genes that are identified in another's patent.

SOURCE: Office of Technology Assessment, 1994.

Box 3-F -- Unpatented Discoveries: Hybridomas, Penicillin, and Fruit Flies

Hybridomas are special types of hybrid cells. The immune system response that protects an organism against foreign substances is a cooperative effort among several types of cells, resulting in a complex series of events involving the production of antibodies and lymphokines. In the early 1970s, scientists became increasingly interested in the function of these antibodies, and their role in the immune response. Cesar Milstein and Georges Kohler, working at the Medical Research Council's (MRC) Laboratory of Molecular Biology in Cambridge England, undertook a study to determine the origins of antibodies. The major discovery, in 1975, was of a technique to produce a special hybrid cell that produces one specific type of antibody and was, in the words of one of the inventors, a "lucky circumstance," but one with profound effects for biomedical research and commerce. Thus, Milstein and Kohler described a technique, based on cell fusion, to produce a hybridoma, which is capable of indefinitely proliferating and secreting large amounts of one specific antibody, referred to as a monoclonal antibody (Kohler, 1975; Kohler, 1976).

Over the following years, the availability of large supplies of monoclonal antibodies revolutionized basic research, medicine, and commercial biotechnology. Monoclonal antibodies are reagents that are easily standardized and provide reproducible results; these substances have been adapted to clinical and home test kits, such as pregnancy diagnostic kits. There are many monoclonal antibodies in development for their potential use as therapeutic agents.

Given the impressive and dramatic commercial and research applications for hybridoma technology, it is noteworthy that the fundamental hybridoma technology was not patented. The decision not to patent the discovery has to be viewed in context of the mid-1970s and non U.S. patent procedures which do not allow any form of publication prior to patent application, and not with the benefit of hindsight. The MRC brought the discovery to the attention of the National Research and Development Council (NRDC), the government funded agency responsible for managing the intellectual property rights arising out of U.K. government-funded research. A patent for the hybridoma was not sought because, i) NRCD's patent council believed that natural living organisms,

including cells in vitro were not patentable (Gibson, 1994), ii) the industrial utility of the research had not been fully recognized prior to publication of the research findings, and iii) at a time when few, if any, biological processes has been patented, there was uncertainty as to the nature of claims that might be made (Owen, 1994).

The technique was immediately and readily available as a result of publication by Milstein, et. al. in *Nature*. Researchers could use the basic technology as published without obtaining permission or paying licensing fees. In addition, researchers could commercialize and patent further discoveries without fear of infringement. The MRC, U.S. researchers, and researchers throughout the world have now filed an extensive array of patents on specific monoclonal antibodies, some based on improvements to the hybridoma technology, others on technology to yield monoclonal antibodies independent of hybridoma technology, and on specific, defined individual antibodies or groups of antibodies.

On the other hand, the failure to patent the technique, especially with the benefit of observing 20 years of explosive commercialization of biology, serves as a reminder to seek patents on new research findings. Opportunities for large monetary profit from basic discoveries come infrequently. From the U.K.'s perspective, the hybridoma experience has had a major impact on government patent policy; no one wants to miss such an opportunity in the future. In small part, the U.K. government's decision to patent ESTs was influenced by the hybridoma experience.

Hybritech succeeded in patenting the logical use of hybridomas, i.e., the use of hybridomas in immunoassays, and succeeded in preventing other companies from commercializing this technology (Hybritech, 19??). Presumably, if the NRDC held the patent to hybridomas and their use in immunoassays, they could have licensed any number of companies to produce these assays. Instead, Hybritech obtained exclusive rights and chose to dominate the field.

Another discovery not patented is penicillin. British researchers conducted experiments using penicillin and arguably "discovered" it in the 1930s, but did not patent it at that time. Consequently,

as no private company could obtain an exclusive position, the findings were not developed. Hence, society did not benefit from the lifesaving attributes of penicillin for almost 15 years; not until wartime were public funds devoted to development of penicillin. The later, improved drugs were patented and the basis of major financial success. Thus, not only does patenting provide the potential for profit, but it also benefits society by driving development of improved therapies.

The workhorse of classical genetics was *Drosophila*. Although fruit fly geneticists developed these creatures into standardized strains at the cost of much time and painstaking effort, no one had attempted to patent them; indeed, fruit fly stocks have been freely exchanged among genetics laboratories on an international basis. Another example is bacteriophages in the middle third of this century, which were also standardized and made widely available among geneticists (Fink, 1993; Kohler, 1994).

SOURCE: Office of Technology Assessment, 1994

Box 3-G Transgenic Animals and Licensing Issues

Transgenic animals, animals whose DNA is augmented by DNA from another species (usually different animals or human), are currently used in biomedical medical research to study a variety of diseases, including Alzheimer's disease, cystic fibrosis, colon cancer, neoplastic diseases, and a number of cardiac diseases. Scientist also report progress in using transgenic animals, primarily pigs, for xenotransplants (Raeburn, 1993).

Many private companies are developing transgenic animals for medical research. For example, Pharmaceutical Proteins, Ltd. (PPL) has developed transgenic sheep that produce an emphysema drug in their milk (Moffat, 1993). Genzyme has developed transgenic goats that express recombinant human antithrombin (AT-III). GenPharm deals primarily with the application of transgenic animal technology to human health care products. GenPharm holds two NIH grants to use transgenic animal technology to produce human antibodies for use in antibody-based therapies for immune and cardiovascular diseases, inflammation, allergies, and cancer (Biotech Patent News, 1993). Companies that develop and maintain transgenic animals receive patents on the animals. Basic researchers who want to use transgenic animals in their research must buy the animals at relatively high cost from the private companies that produce them. For this reason, Jackson Laboratory a government-sponsored facility in Bar Harbor, Maine operates a nonprofit clearinghouse to produce transgenic mice at cost to basic researchers.

Jackson Laboratory established the transgenic animal program in response to requests from biomedical researchers who were frustrated with the high cost of obtaining transgenic animals for use in research. The laboratory set up an international clearinghouse for genetically engineered mice used in the study of human diseases; new strains of mutant mice are sent to the lab by scientists who want to allow their inventions to be distributed to other researchers at low cost and with no patent or license restrictions. The lab accepts mice that are of the broadest use to the research community, and only accepts mice that are freely available to basic researchers. None of the mice kept by the lab have legal restrictions on who can obtain them, how they can be used, or whether the researcher can breed

the animals. Nonprofit health groups and NIH financed the lab's start up costs (Wilke, 1994). The facility breeds and exports mice to national and international labs, in the hopes that research will proceed more rapidly and cures be found more quickly if researchers are not restricted by financial or legal constraints.

The transgenic animal arrangement helps researchers to avoid spending a large portion of their research budget on buying transgenic mice. Researchers and the Jackson Laboratory argue that transgenic mice are not profitable to produce because often a specific mouse must be created for a single line of research. Thus, while it is cost-efficient for private companies to produce transgenic mice that have a wide range of applications and therefore appeal to a large market of buyers, there is no profit incentive for a company to develop specific transgenic mice of use to only a few researchers. Jackson Laboratory provides specialized mice that are not in as high demand as the transgenic mice from private companies.

Although it appears that Jackson Laboratory's transgenic animal facility can coexist with private companies that market transgenic animals without being in direct competition, problems have arisen. The Harvard mouse provides one example of conflict between basic researchers, who need to use a patented invention to perform basic research, and the patent holder who has invested money to develop a technique.

In 1988, Harvard obtained a patent on Oncomouse and then licensed it to E.I duPont de Nemours & Co (duPont). DuPont's licensing agreement contained a "reach-through" provision that required royalty payments on sales of products that were developed, in part, through use of the mouse, even if the mouse was not incorporated into the final product. It also retained full rights for duPont in any research discoveries made with the mouse (Goad, 1993). This requirement had a chilling effect on the use of oncomouse in research, as researchers were unwilling to accept such extreme conditions (Goad, 1993). Eventually, duPont was forced to eliminate the reach-through provision from its licensing agreement in order to obtain licensees (Chen, 1993).

Another example of a restrictive licensing agreement that market forces overturned was GenPharm's policy of preventing breeding of its transgenic mice. Originally, GenPharm did not allow any breeding of its transgenic mice once a pair had been purchased. After much outcry from the research community, GenPharm agreed to allow breeding of the mice for a \$1,000 fee. However, other companies, such as Stratagene and HRP, still prohibit breeding of their mice (Chen, 1993).

On December 29, 1992, PTO granted three new transgenic mouse patents. The patents went to GenPharm, Ohio University, and Harvard University. Taking into account 1993 patents issued, PTO has issued a total of six transgenic animal patents. There is a notable change in the claims from the first Harvard patent to the last three patents: the first Harvard patent claims application to all transgenic oncomammals, whereas the later patents claim applications only in a particular species. PTO says genetic engineering on animals is unpredictable, so inventors should only be permitted to claim application to species on which experiments have already been done (Burke, 1993). As of January 14, 1993, PTO was considering 285 applications involving animals (Lehrman, 1993).

The tension between private research suppliers and researchers for transgenic animals raises the policy issue of whether society can or should continue to rely on public pressure alone to influence equity in licensing agreements. Market pressure also may be a significant factor in forcing adequate licensing access

SOURCE: Office of Technology Assessment, 1994.

Box 3-H *Taq* Polymerase Licensing

The polymerase chain reaction (PCR) is a powerful amplification technique that allows minute quantities of a specific sequence of DNA to be replicated millions of times. Because PCR yields large amounts of DNA on which to perform numerous subsequent procedures from a small amount of original sample, it is one of the most important tools of modern molecular biology (Aldhous, 1993a). The widespread use of PCR as a research tool, however, has been hampered by restrictive licensing and royalty regulations on the PCR process and on a key enzyme needed for PCR called *Taq* polymerase (Hoffman, 1992). The saga of PCR provides an example of the interplay of patenting strategies and commercial and academic research needs. It also paints a negative image of the biotechnology sector as being primarily concerned with using patents to force maximum payments and cumbersome licensing restrictions.

PCR was invented in 1983 by a scientist at Cetus Corp., a biotechnology firm based in Emeryville, CA. Kary Mullis, the employee who conceptualized PCR, won the 1993 Nobel Prize in chemistry, while Cetus Corp. received more than 40 patents covering the PCR process (Wall Street Journal, 1990; Rensberger, 1993). Recognizing the huge potential market for PCR the Switzerland-based pharmaceutical company Hoffmann-La Roche Inc. bought the PCR patents from Cetus Corp. in 1991 for \$300 million in cash plus additional royalties if certain sales levels were exceeded (Lore, 1991; ASM News, 1991). Hoffmann-La Roche planned to license the PCR technology to other companies, and to develop and market clinical laboratory testing services and diagnostic test kits (ASM News, 1991). Hoffmann-La Roche predicted that sales of all DNA-based products for diagnostic purposes would grow to between \$750 million and \$1 billion by the end of the decade, and it formed a subsidiary entitled Roche Molecular Systems Inc., in Alameda, California, to develop PCR diagnostic products (Hoffmann, 1992; ASM News, 1991).

Commercial laboratories wishing to use the PCR technique for the development of diagnostic genetic tests were forced to seek a license from Roche Molecular Systems Inc., which included a down payment of \$15,000 yearly against royalties (Hoffman, 1992). For organizations performing

diagnostic genetic tests, the PCR royalties added about 15 percent to the cost of each test performed (Hoffman, 1992). These fees discouraged many laboratories from seeking a license, and consequently some say the fees discouraged the development of new genetic tests (Hoffman, 1992). The duPont Company had made a “substantial investment” in the development of PCR-based kits for the diagnosis of human diseases, however, because Cetus had licensed all diagnostic uses of PCR to Hoffmann-La Roche, duPont could not obtain a license (Gershon, 1990). In August 1989, duPont filed a law suit against Cetus challenging the validity of its two key PCR patents (awarded in 1987) which cover the PCR process and the detection of PCR products (Gershon, 1990). DuPont cited two sources suggesting a possible method for DNA amplification written more than ten years before Cetus first described PCR (Nature, 1989). In August 1990, the U.S. Patent and Trademark Office (PTO) reaffirmed the validity of the two Cetus patents at the request of Hoffmann-La Roche (Wall Street Journal, 1990; Gershon, 1990).

In 1992, Roche Molecular Systems Inc. announced that it would relax the restrictions and reduce the royalties paid by nonprofit laboratories using PCR for diagnostic and other tests (Hoffman, 1992). This decision may have been a reaction to increased negative publicity in the research community and to potential competition from a new, rival amplification technique called the ligase chain reaction (Aldhous, 1992). The new licensing agreement announced included permission to use PCR for a broader range of applications. Licenses will be available to all academic and commercial laboratories who request them, and academic and nonprofit licenses will require no down payment or minimum royalty payments and a royalty rate of less than 10 percent. The industry royalty rate was set at 15%. The removal of these restrictions was expected to increase the diagnostic use of PCR and perhaps Roche’s royalties as well (Hoffman, 1992).

In addition to licensing PCR, separate licensing and litigation battles have taken place over the use of *Taq* polymerase, a key component of the PCR process. *Taq* polymerase is a thermostable enzyme isolated from the bacterium *Thermus aquaticus* that catalyses the DNA amplification. In December 1989, a broad patent covering the enzyme was issued to Cetus Corp. (then subsequently

sold to Hoffmann La-Roche), which covers purified *Taq* polymerase isolated from the bacterium or derived from a genetically engineered organism (Gershon, 1990; Gershon, 1993a; Seppa, 1993). Because Hoffmann-La Roche lacks a distribution network to market reagents to the research community, it formed a strategic alliance with Perkin-Elmer, a U.S.-based analytical instrument maker with an extensive network of contacts with research labs worldwide, to develop PCR products for research purposes outside the clinical diagnostic market (Aldhous, 1992; ASM News, 1991). Hoffmann-La Roche licenses the human therapeutic and diagnostic fields. Perkin-Elmer licenses all nonhuman fields, including animals. Perkin-Elmer believes that it can command the same fees in the nonhuman areas as Hoffmann-La Roche can for the human areas, despite market realities. Perkin-Elmer has sole rights to sell *Taq* polymerase for use in PCR and markets its *Taq* polymerase as AmpliTaq® (Aldhous, 1992).

In countries where Hoffmann-La Roche's patents are valid, researchers who want to use PCR are legally obliged to buy AmpliTaq® from Perkin-Elmer (Aldhous, 1992). Perkin-Elmer also requires licensees to purchase their machines to use PCR, regardless of whether or not it is useful in the licensees' process. The royalties on AmpliTaq® add up to hundreds of thousands of dollars a year for some laboratories (Aldhous, 1993b). Several companies, including Promega Corp., a research biochemicals supplier in Madison, WI, possess licenses to manufacture and sell *Taq* polymerase only for non-PCR uses, such as DNA sequencing (Aldhous, 1992). These companies sell *Taq* polymerase to academic laboratories at discounts of up to 60 percent of Perkin-Elmer's prices for AmpliTaq® (Aldhous, 1992). Though these suppliers may not mention the utility of *Taq* polymerase for PCR in their promotional material, it is general knowledge that up to 85 percent of their sales are to customers who use the enzyme for PCR (Aldhous, 1992). In 1991, several reagent companies had pursued particularly aggressive marketing of *Taq* polymerase in Europe, where the European Patent Office hadn't yet issued PCR patents to Hoffmann-La Roche. Perkin-Elmer, therefore, commanded less than half of the \$26 million 1991 *Taq* polymerase market (Aldhous, 1992).

In early 1992, Hoffmann-La Roche began to confront companies around the world that were

selling *Taq* polymerase to PCR users without licenses to sell *Taq* polymerase for non-PCR uses (Aldhous, 1992). At least two companies stopped distributing *Taq* polymerase after being contacted by Hoffmann-La Roche (Aldhous, 1992). In October 1992, Hoffmann-La Roche announced it was suing Promega Corp., alleging that Promega had breached its 1990 license agreement that allowed the marketing of the enzyme for only non-PCR uses (Aldhous, 1992; Gershon, 1993a). Promega countersued in April 1993, challenging the validity of Hoffmann-La Roche's *Taq* polymerase patent (Gershon, 1993a). Promega cites evidence that *Taq* polymerase purification from *Thermus aquaticus* was previously published (Gershon, 1993a). Perkin-Elmer also began to confront researchers who used supplies of *Taq* polymerase unlicensed for PCR, citing a policy to "gently remind users that there are patents that apply to this technology" (Aldhous, 1992). Some Australian scientists reported threats of litigation and heavy pressure from Perkin-Elmer to stop buying *Taq* polymerase from other sources (Aldhous, 1992).

The licensing of *Taq* polymerase raises several issues about the role of patents in scientific research. Public complaints from researchers needing *Taq* polymerase express the view that the patent positions of Hoffmann-La Roche and Perkin-Elmer are "contrary to the spirit of the traditional relationship between industrial and university research and inimical to the philosophy of the patent process, which is intended to encourage innovation" (Sederoff, 1993). Promega's suit claims that "the monopoly of such an enzyme by any one company such as Hoffmann-La Roche has severe implications for scientists" (Seppa, 1993; WI BioIssues, 1993). Promega officials hope that an invalidation of the *Taq* polymerase patent will inspire competitive pricing and allow more laboratories access to the enzyme at lower prices (Seppa, 1993; WI BioIssues, 1993).

Concerned about pressure from the scientific community, Perkin-Elmer agreed in July 1993 to offer discounts on AmpliTaq® to large-scale users, although this unfairly impacts small companies and users. Laboratories ordering more than 250,000 units a year will pay only 24 cents per unit, as opposed to the usual 50 cents per unit (Aldhous, 1993b; Gershon, 1993b). Though this offer was only extended to U.S. laboratories, it was expected to apply to non U.S. laboratories soon. The

company also hoped that cutting the cost of the enzyme will stimulate new applications for PCR (Gershon, 1993b). Additionally, the Human Genome Project's 20 genome centers could receive one free unit for every unit they pay for, if they purchase over 250,000 units per year. In July 1993, Roche allowed Boehringer Mannheim a nonexclusive license, valid for the term of Roche's PCR patents, which provides the company with worldwide rights to make and sell the enzyme for use in PCR in all fields except in vitro diagnostics (Gershon, 1993b).

SOURCE: Office of Technology Assessment, 1994.

Box 3-I -- European Community Directive

The European Union has developed a Directive addressing the legal protection of biotechnological inventions including human genes. The Council of the European Union adopted a common position on February 7, 1994. It is expected that the Council may adopt the Directive before the end of 1994, after the second reading before the European Parliament. The recitals in the Directive recognize the commercial value of biotechnology and genetic engineering, and that uncoordinated development of national laws on biotechnology could result in trade disincentives and impinge industrial development but states that biotechnology does not need a separate regulatory scheme outside of patent law. It also notes that no national or international law precludes the patentability of living matter. In pertinent parts, the recital reads:

(10) Whereas, in the light of the general principle that the ownership of human beings is excluded, the human body or parts of the human body as such, for example a gene, protein or cell in the natural state in the human body, including germs cells and products resulting directly from conception, must be excluded from patentability, but isolated parts of the human body should not be unpatentable merely because of their human origin, it being understood that the parts of the human body from which such isolated parts are derived are excluded from patentability;

(11) Whereas, however, isolated human nucleic acids having no described application other than the expected properties attributable to any such nucleic acid, for example their ability to be used as a probe or as a primer for synthesis of further copies of nucleic acid, should be unpatentable:

(12) Whereas processes for modifying the genetic identity of the human body which are contrary to the dignity of man must be excluded from patentability.

Chapter I, Patentability, Article 2 reads:

1. The subject-matter of an invention shall not be considered unpatentable merely on the grounds that it is composed of, uses or is applied to biological material.
2. Biological material within the meaning of this Directive means any material containing genetic information and capable of self-reproducing or capable of being reproduced in a biological system.
3. Invention shall be considered unpatentable where publication or exploitation would be contrary to public policy or morality; provided the exploitation shall not be deemed to be so

contrary merely because it is prohibited by law or regulation in some or all of the Member States. On this basis, the following *inter alia* shall be unpatentable:

- (a) the human body or parts of the human body as such;
- (b) processes for modifying the genetic identity of the human body contrary to the dignity of man;
- (c) processes for modifying the genetic identity of animals which are likely to cause them suffering or physical handicaps without any substantial benefit to man or animal, and animals resulting from such processes.

There are inherent contradictions in the provisions of the Directive. The controversy surrounding these provisions may delay resolution and adoption.

APPENDIX to CHAPTER 3: Issues Raised by NIH Patent Applications

As mentioned in chapter 2, in 1991 the National Institutes of Health (NIH) filed for patent protection on more than 300 human gene fragment sequences--referred to as expressed sequence tags or ESTs. In all, NIH's application encompassed more than 6,000 ESTs. In fall 1992, NIH announced that PTO had rejected NIH's initial application because it lacked novelty, lacked utility, and was obvious; NIH responded to PTO's initial rejection in February 1993, but in February 1994, NIH withdrew the entire EST patent application. Although NIH withdrew the application, it challenged conventional thinking about the elements of patentability for human DNA sequences.

Utility

As mentioned earlier, to meet the utility requirement an invention needs at least one practical use. As applied to ESTs, such sequences could meet the utility requirement because the practical utility requirement is a low threshold to clear (Bent, 1992) and several potential utilities that could be claimed in an EST patent application exist. For example, EST might be useful in isolating the corresponding full gene. A scientist might thus be able to manipulate the full gene and ultimately express, in vitro, the protein product from that gene. In addition, ESTs could be useful as genetic markers or probes. They could be used to mark the presence of the full gene of which they are part, which could be helpful to map the genome generally, or, in some cases, to locate disease genes specifically. Finally, ESTs could be used to construct so called antisense versions of the full gene sequences from which they derive, which could be used to block the expression of the product or related gene products--thus, providing the possibility of therapeutic applications for gene products that cause disease. One question, then, is whether an application with ESTs that asserts utility, without actually demonstrating that each claimed EST can be useful as a probe or marker, will be granted (In re Bell, 1993). Some experts contend that the utilities recited in the NIH applications, though admittedly not the primary or major utility for the claimed sequences, are more substantial than the "object of researchers' interest" utility rejected in *Brenner*, since the EST was associated with a specific tissue, it assured the use of the EST in question a forensic utility as a marker for human brain

tissue. Accordingly, the sequences provide access to polypeptide encoding sequences within the genome.

Novelty

Drawing from experience in the area of chemical and biological inventions, a patent application must describe a stretch of DNA that has not been previously patented, published, or practiced in the prior art. Case law dating back to 1912 held that an isolated and purified version of a natural substance is new (and therefore meets the standard of novelty) even though it existed mixed with other natural products in the human body (Merges, 1993b). Isolated insulin, adrenaline, and human growth hormone are examples of natural body products that have been patented when prepared by humans in purified, and hence, novel forms. In these cases novelty was conferred by the absence of contaminants. ESTs could clear the novelty hurdle because they are compositions of matter that have been isolated from natural materials through human intervention and are distinguishable from an element of nature under U. S. patent law. A researcher who clones a human gene arguably has created a new composition of matter by identifying something that previously only existed within a human cell which makes the isolated sequence readily available for further applications. Isolated sequences can be used to make copies for sequencing and study, to produce large quantities of the corresponding protein in a purer form, or as a therapeutic or diagnostic reagent, itself (Eisenberg, 1990).

PTO has stated that “a nucleotide sequence lacks novelty when the sequence sought to be patented is the same as [has the same bases as] a nucleotide sequence known to the public at the time the invention was made. When a claimed sequence differs from that which is known by one or more bases, the question of obviousness must be considered. Whether or not a different but similar sequence is unobvious is a question that must be resolved on a case-by-case basis” (Van Horn, 1994). The EPO regards one change from a prior sequence as sufficient to impart novelty.

Nonobviousness

According to the patent statute, an invention may not be patented if it would have been obvious, in light of existing knowledge, to a person having ordinary skill in the field. Whether DNA sequences are “nonobvious” presents a legal question of some complexity.

When asked whether a sequence defined in a claim of a patent application is patentable in light of known DNA sequence information, PTO responded “there is no threshold of sequence similarity between a claimed sequence and a sequence in the prior art that would automatically qualify any particular prior art reference as being a proper basis for an obviousness rejection There is no threshold level of similarity for determining whether a given sequence in the prior art would render a claimed sequence obvious because it is the particular nature of the differences that is important, and what was known about the consequences of those differences by those skilled in the art at the time the invention was made. For example, a single difference in a nucleotide base may make no difference in the properties of the DNA or the protein coded for by the DNA. If the single difference occurs at an active site, however, significant difference in the DNA and/or biological properties of the resulting protein may occur. As with other chemical compounds, the differences in the biological properties of the DNA molecule or a protein molecule must be considered in conjunction with the differences in the structure (sequence) per se, when determining the obviousness of a new DNA molecule relative to a known molecule” (Van Horn, 1994).

One case that may be relevant to the scope of EST patent application claims is the recent case of *In re Bell* (991 F.2d 781). In *Bell*, a patent application claiming human DNA sequences that code for human insulin-like growth factors I and II (IGF-I and IGF-II) was rejected by an examiner on the ground of obviousness. The examiner cited two prior art references, each of which disclosed amino acid sequences--essentially, the protein structure--for IGF-I and IGF-II, along with a general source describing patented cloning techniques. The Federal Circuit Court reversed the examiner’s rejection of the claims and held that the nucleotide sequence was not obvious based on the knowledge of the amino acid sequence of the protein encoded by the nucleotide sequence--even though the party knew the method by which to obtain the sequence (Bell, 1993). The court reasoned that although one

reference provided the structure of the protein, a multitude of possible nucleotide sequences could code for the amino acid chain cited in the reference (991 F.2d 781, p. 784). Thus, given the astronomical number of possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities is the human sequence, the claimed sequences would not have been obvious. In addition, the general reference on gene cloning did not expressly teach nor fairly suggest that its general method for isolating genes should be combined with the protein sequence of the other references. By this reasoning, however, the only nonobvious sequence was the authentic human one, and other sequences derived from the genetic code would not infringe--if not directly then under the reverse doctrine of equivalents.

The nonobviousness standard encourages researchers to pursue projects for which success appears highly uncertain at the outset and influences the decisions of research and development managers to pursue or ignore specific research projects (Merges, 1993a). Thus, even if one skilled in the art could know in general how to create the claimed ESTs, the highly empirical nature of the actual work, i.e., the uncertainty of any particular result, argues in favor of patentability.

Still, because the obviousness of an invention is measured against the background of human knowledge at the time the invention is made, this requirement is increasingly difficult to pass as scientific knowledge advances in a field (Eisenberg, 1992). What is not obvious today would well be obvious tomorrow. Even if NIH's application and subsequent sequence publications alone do not render obvious all related genes and gene products, it is entirely possible that subsequent inventors who find useful genes and gene products related to the partial sequences will be unable to patent their inventions because other intervening advances will make their inventions obvious by the time they are made (Eisenberg, 1992). As a practical matter, obviousness rejections are hard to overcome. Once a technology is patented, for example transgenic animal technology, as a new inventor must prove the results on the experiment were unpredictable (O'Farrell, 199?). On the other hand, others have expressed confidence that researchers will be able to create innovations and their patent lawyers will draft claims substantial enough to merit patent protection even as the level of skill in the art continues

to rise (OTA Legal Workshop, 1993).

Because the obviousness standard is unrelated to the amount of intellectual effort actually expended making the invention, many researchers believe it unfair to allow patents on results of DNA automated sequencing, since the intellectual effort involved is minimal (OTA International Workshop, 1993). However, patent law's purpose is to "promote the progress of science and the useful arts," not necessarily to reward hard work with intellectual property rights, while disallowing patents for work discovered through minimal labor. The law is clear that patentability is not negated by the manner in which the invention was made (35 U.S.C. § 103). Just because an invention is easy to do does not mean it is obvious.

The impact of the obviousness standard can be elucidated by examining patent claims. For example, early DNA patents often claimed, and were granted, a broader scope than later applications. This stems from the nature of U.S. patent law, which is self-correcting--i.e., prior art constrains the breadth of future claims (Baker, 1993). Patents issued today allow PTO grounds for rejection of broad claims in future patent applications; only narrow claims in the field will succeed. That is, because of the nature of prior art and obviousness, subsequent discoveries in the same field receive a more narrow scope. For example, the Harvard mouse patent claimed the field of transgenic nonhuman oncomammals, whereas recent patents on transgenic mice were only permitted to claim oncomice.

With respect to the NIH applications, a gene of unknown function, could identify a gene of known function. Thus, granting a patent claiming thousands of ESTs with broad claims to the entire gene and gene products would effectively place control of major portions of the genome into the hands of an individual or company--a notion that many find objectionable.

On the one hand, an EST sequence might clear the nonobvious standard because there was no reasonable expectation of success. On the other hand, PTO might rule that an EST sequence is nonobvious because there was no reasonable expectation that the invention would succeed, the

invention required undue experimentation, or if the prior art pointed to a promising field of experimentation but did not provide further guidance. Of import to PTO's decisionmaking is whether the claimed invention could be reasonably predicted on the basis of prior art. For example, it might be that any newly identified DNA sequences will be deemed obvious if they have been derived using standard techniques (Eisenberg, 1990). Others suggest that § 103, "patentability is not negated by the manner in which the invention was made" is controlling. Automated sequencing (robotics) technology make it routine and straightforward, but not obvious. The intellectual work comes with library selection, preparation, and generation, the steps prior to the actual sequencing.

Disclosure

As mentioned, one key issue raised by the NIH application is the extent to which partial DNA sequence disclosure becomes prior art to the full length sequence of a gene.

Enablement Recent court decisions suggest that merely describing how to obtain a DNA sequence or elucidating the DNA sequence is insufficient to support a claim to the entire gene, either on the grounds that the claim is not supported by an adequate description, that it is not enabled, or that the inventor has not fully conceived of the invention (*In re Bell*, 1993). Thus many lawyers maintain that if an EST patent application asserts rights to the entire gene, the claims are too broad given that the only disclosure is a fragmentary gene sequence. They argue that in order to claim the entire gene, one must sequence the entire gene. In fact the 1993 decision in *In re Bell*, the Court of Appeals for the Federal Circuit noted that a general reference to cloning techniques did not disclose or teach the method to isolate and combine DNA sequences specific to the claimed invention. Put another way, the invention was not properly enabled.

In light of the disclosure requirement, it might seem logical to limit the rights of a patentee to only those embodiments of the invention that are disclosed in the specification, i.e., those that are actually created at the time the patent application was filed. Such a rule, however, would soon render patents useless (Merges, 1993c). Thus it is widely recognized that a patent's specification need not

point out precisely how to make every device that would fall within its claims. Disclosure of an inventive concept or principle, whose precise contours are defined by the claims, is enough.

For example, in 1991, the Court of Appeals for the Federal Circuit ruled on the scope of claimed invention in *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* Amgen held a patent on recombinant DNA erythropoietin (EPO) which is used to stimulate red blood cell production. One of the claims granted to Amgen covered all possible DNA sequences encoding a protein sufficiently duplicative of EPO to have the property of increasing the production of red blood cells. The district court found that substitution of a single amino acid position resulted in over 3,600 EPO analogs, and substitution of three amino acids could result in over a million different analogs. The district court declared that Amgen did not enable its broad claim because it did not disclose particular analogs and how to make them. Since Amgen only disclosed how to make a few analogs, it was not entitled to claim all of them.

Experts argue that the Federal Circuit Court's holding in *Amgen* appears to warrant a finding that claims to the complete DNA sequences or expression products based on ESTs would be improper because the claims are trying to reach a myriad number of DNA sequences, based on an enablement of a smaller number of sequences, the smaller number having been shown capable of producing a desired expression product (Merges, 1993c). That is, just as in *Amgen*, applicants could face problems claiming subject matter beyond the raw sequence data; claims to "any EST that hybridizes with a gene," for instance, might be nonenabled.

In the same opinion, the court rejected a challenge to Amgen's patent based on an alleged prior invention of the EPO gene by another scientist who first thought of an approach to find the gene. The court stated that knowing the process to obtain the DNA sequence that encodes a protein is insufficient to claim patent rights to the gene before the actual sequence is known; one must actually perform the process and obtain the DNA sequence. *Amgen* may not be predictive of whether EST patent applications would be granted. Today's state of the art is considerably different from the science at the time *Amgen* was considered.

Prior Art. An unresolved issue is the availability of ESTs as prior art against subsequently sequenced genes. Has the state of the art reached the level where it is routine to obtain a complete gene once the EST for it is available (In re Wands, 1988)? The raw sequence data generated in the NIH application was published immediately, making it available as prior art against future patent applications. Publication includes disclosures of DNA sequence information in grants, and on Internet databases. However, PTO would face difficulties in tracking whether a sequence has been described via Internet, so practically speaking, it does not pose a barrier to exchange of information. Depositing DNA sequence information in GenBank also constitutes publication, although GenBank will hold sequence data until a specified release date. Once the researcher places the data in GenBank, he or she relinquishes ownership of the sequence data.

The critical issue is whether the prepublication of a single EST would render obvious later filed claims to the entire gene, or whether it is necessary for patent applicants to try to obtain claims for the whole gene as soon as they have the EST in hand. To the extent the NIH applications claimed subject matter for which patentability was questioned by publication (i.e., by the presence of this data in the prior art), early filing would preserve the patentability of subsequently developed subject matter. Most importantly, early filing of claims to raw sequences could preserve later claims to full genes and their protein products. Such additional subject matter could be added to the patent application during its pendency, and perhaps entitle the inventor to claim the original filing date of the raw sequences as his priority date, in effect preserving patentability despite scientific publication of the raw sequences. Technically, the full genes and their related proteins would be entitled to the priority date of the raw sequence filing only if not considered “new matter” (35 U.S.C. § 120). If the full genes and their related proteins were considered new matter, it would imply that they were not described in the application and were not anticipated by that description. It does not necessarily mean, however, that the full genes would not be obvious from the subject matter described in the application. In general, the existence of a partial sequence in the prior art does not destroy the patentable novelty of a full gene sequence, if the new sequence has different biological properties. And, as previously noted, (e.g., *Bell*) courts have not yet concluded that gene-protein relationships are so well-established that

knowing the structure of one renders the other obvious. Hence, the partial structure might not create obviousness problems for later claims for either the full gene or its related protein. On the other hand, each case is different and, as just mentioned, the growth of knowledge in biotechnology could lead courts to apply the nonobviousness standard more stringently, so that a full gene or protein could be considered obvious in light of a partial sequence in the prior art.

Even if the presence of partial sequences in the prior art causes problems for the patentability of full genes and related proteins, certain claiming strategies could allow an applicant to circumvent the problem. It is possible to obtain a commercially viable patent for a gene and protein even if prior art precludes the most desirable claiming formats.

In 1992, the Board of Patent Appeals and Interferences decision in *Ex parte Ishizaka*, suggested that published ESTs might be prior art to future claims to full length gene sequence discoveries. The Board held that if sequences are published, the full length gene would be deemed obvious and therefore unpatentable. Thus, it left open whether a published EST would create difficulties in obtaining a patent on a gene incorporating several ESTs.

Written Description. In 1993, in *Fiers v. Sugano*, the Court of Appeals for the Federal Circuit ruled that in order to establish patentability of a gene and claim the protein product, the applicant must disclose the entire DNA sequence for the gene. At issue in *Fiers* was the adequacy of the written description and incomplete conception of the invention; *Fiers* shapes the written description problem. In *Fiers* the claim to the full gene was rejected for lack of a complete written description. The court held that merely knowing how to isolate the gene is not sufficient to claim the entire gene or its encoded protein. The inventor must know the detailed structure of a gene to claim it.

Recent events show the direction of patent for gene discoveries. Scientists discovered a human tumor suppresser gene (Service, 1994). A possible sequence for a candidate gene was inferred from a microbial analog. The researchers sought the EST from the private files of a company, with an

arrangement with the company (Weiss, 1994). The identification of an appropriate EST was the critical step in finding the gene. The researchers gave the company whose ESTs they used the first rights to commercialize the discovery through an exclusive license, in turn for having access to the ESTs (Macilwain, 1994).

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CHAPTER 4

ETHICAL CONSIDERATIONS

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Patenting human DNA sequences potentially raises several ethical and moral issues; What is the ethical rationale for allowing or disallowing patents of biological materials such as DNA? Is there a difference between patenting human animal, or plant DNA? Could patenting human DNA be tantamount to owning humans? Is asserting property rights in humans a necessary cost of promoting scientific innovation and commercialization? What is the relationship between human DNA sequences and perceptions of self identity? Do proprietary rights in human sequences affect society's conception of human dignity and common heritage?

Answers to such questions depend, in part, on the scope of rights granted to a patent holder -- both in the past and potentially in the future. This chapter examines the ethical, social, and philosophical implications of patenting human DNA sequences in light of existing patents on microorganisms, transgenic animals, and certain human DNA sequences (e.g., full genes). It discusses the U.S. history that shaped today's debates, as well as international perspectives.

HISTORICAL CONTEXT OF ETHICAL DIMENSIONS

The ethical debate about patenting human DNA sequences has roots in similar discussions about patenting microorganisms and animals (OTA, 1989), but also takes a different form because human matter is involved. To place the ethical analyses in context, this section briefly reviews the historical events that shaped today's controversies (box 4-A).

The Early Debate

In 1980, the U.S. Supreme Court ruled in Diamond v. Chakrabarty that a live microorganism is patentable as a new and useful composition of matter (Diamond, 1980). This concept was extended in 1987, when the Board of Patent Appeals and Interferences ruled that a nonnaturally occurring, nonhuman animal (an oyster) was patentable (Ex parte Allen, 1987) and when Harvard University received a patent for a genetically engineered mouse (U.S. 4,736,866) in 1988. These actions touched

off an extensive dialogue on the ethics of patenting living organisms (OTA, 1989), and many of those issues reappear in the current debate surrounding patenting human DNA sequences.

Colliding with the concerns about patenting living organisms were questions that surfaced in 1986-87 about intellectual property protection of DNA sequences--with initial attention on copyright protection--from what would become known as the Human Genome Project. Even before government funding was approved, Nobel laureate Walter Gilbert announced he was starting a corporation to decipher the human genetic code (Davis 1990; Cook-Deegan, 1994), with income to be derived from copyrighting the sequences and subsequent selling of the information.

Still, discussions of intellectual property issues focused largely on issues related to data sharing and collaboration. The National Research Council's 1988 report on the Human Genome Project recommended that "human genome sequences should be a public trust and therefore should not be subject to copyright" in order to enhance scientific collaboration (NRC, 1988). As noted in chapter 2, OTA judged that genome projects raised no new questions of patent or copyright law (OTA, 1988), but also noted the importance to the Human Genome Project of prompt and full datasharing. Similarly, in 1988 the American Society of Human Genetics solicited comments for a policy statement on the claim that human genome sequences should not be subject to copyright, but be placed in a public trust to ensure datasharing and collaboration (Short 1988). Three years later, the intellectual property and ethical considerations remained unarticulated: Following a 1991 National Institutes of Health (NIH) conference on the genome project, an NIH steering committee was charged with, among other things, examining whether intellectual property issues "present sufficient internationally relevant ethical issues to deserve a task force" (Capron, 1991)--an unfulfilled recommendation.

The NIH Patent Applications

The discussions of the late 1980s and 1990-91 sharpened considerably in 1991-92. As detailed in chapter 2, beginning in June 1991, NIH filed patent applications on fragments of DNA sequences--

referred to as expressed sequence tags (ESTs) or complementary DNA sequences (cDNAs)--with unassigned biological function, but claiming the EST, the entire gene from which it derived, and the protein product of this gene as deserving protection (Roberts, 1991; Roberts, 1992). The British Medical Research Council argued against granting such patent rights, but followed suit with a similar application in July 1992, stating it did so to ensure involvement in the debate and also to avoid being at a competitive disadvantage should the NIH patent application be granted (Aldhous, 1992). Suddenly, several issues related to intellectual property protection and human DNA, including ethical considerations, were thrust to the forefront.

In contrast to legal discussions about the patentability of DNA fragments, opposition on ethical grounds surfaced against the generic concept of patenting any human DNA sequences, including whole genes. Representative of this opposition is a statement adopted at the May 1992 North-South Human Genome Conference in Brazil:

This work has to be done with great respect for human dignity and with the understanding that the knowledge obtained should be the prized possession of all humanity. In order to reap those benefits it is essential to achieve a balance between the protection of intellectual property rights and the free exchange of information and materials needed for optimal international collaboration in carrying out the Human Genome Project. In order to achieve the desired balance, we urge that consideration be given to avoiding the patenting of naturally occurring DNA sequences. The protection of intellectual property should, in our opinion, be based on uses of sequences rather than on sequences themselves (McKusick, 1992).

Clearly, representatives at this conference opposed patenting whole gene sequences (as well as fragments) as composition of matter, although certain intellectual property rights--i.e., use patents--would be allowed. Furthermore, in addition to the familiar reason of fostering international collaboration, this statement introduces additional themes on respecting human dignity and on genomic knowledge being the prized possession of all of humanity (box 4-B).

WHAT MORAL QUESTIONS ARISE FROM THIS HISTORY?

Experts have offered several policy options to address concerns such as those raised in the North-South Genome Conference. For example, for questions on whether such patents would impede scientific collaboration and progress, certain technical changes to patent law could mitigate these problems--e.g., an experimental use exemption (Eisenberg, 1990; 1992)--so that patent protection theoretically would be fully compatible with unimpeded basic research. Similarly, to allay fears about hindering collaboration and avoid economic exploitation of international research partners involved in the Human Genome Project, NIH maintained it would license its patents in a socially responsible fashion (Healy, 1992). As for allowing only process or use patents but not composition of matter patents involving human DNA sequences, many countries do not recognize composition of matter patents. However, the United States recognizes composition of matter patents, which are considered to offer stronger protection and thus preferred in the U.S. system.

Still, beyond such practical matters, the history of patenting living organisms when juxtaposed with the NIH patent applications clearly elicited an array of questions; many cast broadly as having a moral or ethical base. Among the questions raised when NIH sought intellectual property protection for ESTs were:

- Is it appropriate to patent an EST, provided one believes the work is mechanical and offers no knowledge that is directly useful (Roberts, 1991; 1992a; 1992b)?
- Will a patent for an EST hinder the free exchange of scientific ideas at an early stage of their development and interfere with their fuller articulation over time (Roberts, 1991; 1992a; 1992b; ASHG, 1991; McKusick, 1992)?
- Will the publication of information about ESTs without patenting them prevent others from receiving patents on an entire gene sequence once it and its function are identified (Healy, 1992)?

These questions, however, while important, are not primarily moral issues for which moral reflection is particularly relevant. The first question raises the policy issue of what type of work a patent should reward. The second question raises the empirical puzzle of the extent that patents interfere with scientific cooperation and progress, and whether a research exemption of other

modifications in patent law can limit the extent of this interference. The third question rests in statutory interpretation of patent law. (See ch. 3.)

However, the NIH applications raised other questions with clear moral relevancy, and these questions present ethical issues related to patenting human DNA sequences, generally, not just patenting ESTs. Among such questions are:

- Is it appropriate to patent human DNA sequences if they are viewed as part of humanity's common heritage and so should be in society's custody (Macer, 1991; McKusick, 1992; Council, 1994)?
- Is patenting human DNA sequences compatible with respect for the dignity of human beings and human life (Macer, 1991; McKusick, 1992; Commission, 1992; Commission, 1993; Commission, 1994)?
- Will patents unfairly affect research and commercial efforts in developing nations (Curien, 1992; Herman, 1992)?

European governments--in particular the French government--stressed the issue of universal heritage, and raised the additional matter of the potential negative impact of such patents on developing countries (box 4-C; Curien, 1991).

Context of the Questions

While these questions have implications for policymaking, they are fundamentally moral in nature compared to other questions that involve policy tradeoffs, empirical consequences, or statutory interpretation. The first question presupposes that certain things should be common possessions because there is no private entitlement to them, and asks whether human DNA sequences are among those things. The second question posits the value of respecting the dignity of human beings and human life, and then asks whether patenting human DNA sequences is compatible with that value. The final question assumes some conception of justice in the relation between developed and developing countries, and asks whether patenting human DNA sequences would violate a just order. Thus, even if there are empirical and policy components to these questions, crucial components of

them are moral questions: What things should be the common possession of humanity? How is the dignity of human beings and human life respected? What is a just international order?

To date, although such moral questions have been raised, their underpinnings have received scant analysis in the literature. For example, the first question neither offers a theory of what should be the common possession of everyone, nor explains why human DNA sequences should be part of that possession. The second question raises the issue of human dignity, but arguments are then not articulated as to what constitutes protecting human dignity, nor why patenting DNA challenges that dignity. Finally, the conception of what constitutes a just international order largely remains unexplored (Brody, 1993). What, then, is the context of the issues raised by the questions?

At least four possible interpretations underlie the notion of appropriate, or inappropriate, patenting and a relationship to our common heritage. The first is the issue of whether, from a moral perspective, human DNA sequences and other things that occur in nature--and hence in that sense part of society's common trust--should be patentable when isolated and purified *ex vivo*? Most nations' patent laws contain significant limitations, in part morally based (Brody, 1994), on patenting naturally occurring substances. Put differently, should there be a morally based limitation on patenting human DNA sequences because they occur in nature? Second, independent of patent law, should people be allowed to claim intellectual property protection on things that occur in nature, that they did not produce, and that in some sense belongs to all? Should there be a limitation on the individual ownership of human DNA sequences through patents because all should own them? A third interpretation essentially raises the same issue found in the question of international justice: Given that human DNA sequences are found in all individuals, and in that sense could be viewed as the common heritage of all humanity, is it just that human DNA patents be controlled by the citizens of developed countries (who will certainly be the ones who first obtain the patents) to whom citizens of developing nations will have to pay royalties? Finally, should things that occur in nature, and are therefore part of our common possession, be freely available for research by everyone? With this interpretation, the question raises issues similar to the nonmoral questions about scientific cooperation

and progress, but it does so from a moral concern about the use of our common heritage rather than from a purely consequentialist concern about protecting scientific progress.

For the second core question, which addresses patenting and human dignity, at least four possible interpretations of the concern behind the question also exist. Each interpretation sees the patenting of human DNA sequences as challenging human dignity in different ways. The first interpretation acknowledges that one way of protecting human dignity is by barring the ownership of human beings. Put another way, should the U.S. constitutional prohibition against owning humans prohibit the ownership of human DNA sequences through patents; is such an extended prohibition necessary for, or at least helpful to, protecting human dignity? The second interpretation stems from the observation that many things may not be commercialized--e.g., certain body parts: A widespread, although not universal, ban on the sale of body parts exists, presumably because commercialization cheapens what should be dignified. Should the restriction on selling body parts cover human DNA as well, and is one way to accomplish this through prohibiting the patenting of human DNA sequences? Is commerce in human DNA sequences compatible with a respect for human dignity? The third interpretation flows from the observation that human identity from a species standpoint is connected with genetic constitution at some level. Does protecting genetic identity by prohibiting patents involving human DNA sequences safeguard human dignity, since DNA sequences define, in some measure, what constitutes a human? Should a stranger be able to exercise ownership of genetic structures that define, however partial and at whatever level, the very composition of another individual? The final interpretation assumes that respecting human dignity involves, among other things, protecting the genetic integrity of human beings. Yet, patenting human DNA sequences involves their manipulation and modification; so should patents on human DNA sequences be precluded as a way of protecting genetic integrity?

Regarding the third core question, at least two interpretations underlie the concern about a just order. One notes that tremendous disparities in wealth between developed and developing countries exists and asks whether justice allows for the introduction of additional property rights (patents in

human DNA sequences) that might increase these disparities. A second interpretation involves both the issue of international justice, as well as the issue of common heritage: Is it just that some countries may assert intellectual property rights on human DNA sequences, which some view as the common heritage of all humanity?

Finally, do the moral arguments that address these three core questions apply equally to the different types of patents that can be issued--i.e., for a human DNA sequence as a product, the use of that sequence, or the process of manufacturing the sequence? For example, the starting point for all of the common heritage arguments, and the second of the just order arguments, is that the substance to be patented occurs in nature. But many of the uses that people would want to patent do not exist in nature, so these arguments seem to apply only to patents on the human DNA sequences themselves. Similarly, many of the human dignity arguments again are directed against proprietary interests via patents on the human DNA sequences themselves. But, there are some arguments that might be directed against all three types of patents. The first interpretation of the just international order arguments targets the impact of patents on increasing disparities between the wealth of countries. It assumes granting composition of matter, use, or process of manufacturing patents related to human DNA sequences would exacerbate existing differences; it also assumes that patents and development of novel therapeutics or diagnostics provide no benefit to developing nations. Similarly, to protect genetic integrity by preventing changes or manipulation of human DNA sequences, any type of patent involving human DNA sequences might be opposed. Reviewing the questions reveals that the focus is primarily directed against patents on products, not use patents or process of manufacturing patents--which also explains, in part, why some oppose patents on human DNA sequences, but accept use or process of manufacture patents.

Analogies With Animal Patents

As mentioned earlier, the controversy about patenting human DNA sequences followed on the heels of the controversy about the patenting of transgenic animals. And in fact, it is not unexpected

that the two often are viewed as parts of a single, general controversy. Further, as previously noted, many of the moral questions raised by patenting human DNA sequences were first presented during debates on the ethical implications of animal patents (box 4-D). Hence, the analysis of the issues for the current controversy--presented in the next section--will draw, in part, on the ethical analyses applied in the evaluation of animal patents.

Nevertheless, while the ethical arguments relevant to patenting animals serve as useful background, they are not directly comparable; relying too heavily on arguments from the animal patenting controversy could be misleading. Several fundamental positions that crystallized around the debates on the ethics of patenting animals (Dresser, 1988; OTA 1989) do not apply to patenting human DNA sequences. Likewise, the concerns related to the issue of common heritage have no analog in the animal patenting controversy. Table 4-1 summarizes the analogies and dissimilarities.

ANALYSIS OF THE CENTRAL ISSUES

Overall, at least three core moral issues arise from patenting human DNA sequences. This section analyzes and evaluate these issues.

Issues Related to Common Heritage Concerns

One interpretation of concerns about common heritage focuses on the patentability of things that occur in nature (box 4-E). Regardless of legal justifications, the interpretation can be formulated as two moral issues: Are there moral justifications for intellectual property rights? And, why should anyone be allowed to patent something that they isolated, but that already existed in nature and is therefore not new?

Intellectual property rights--such as patents--can be justified from a moral perspective on at least two grounds. First, they are needed to provide incentives for people to invest in those who will invent. And second, those who labor to make the discoveries deserve the rewards offered by

intellectual property rights (Becker, 1980; Goldman, 1987) because society, as a whole, benefits from the public disclosure of the discovery. Discovering previously unknown, naturally occurring substances by isolating and identifying them is a useful, and resource-consuming activity that might require the same incentives as inventing new, non-naturally occurring compositions of matter. Similarly, those who labor to isolate and identify previously unknown, naturally occurring substances might equally deserve the financial benefits offered by intellectual property rights that accrue to those who labor and invented new compositions of matter. Thus, moral justifications of intellectual property rights exist and can be applied to previously unknown, naturally occurring substances--e.g., human DNA sequences--that have been isolated and identified by scientists.

Nevertheless, how can anyone exert monopoly rights on substances that are part of nature and the common heritage of humanity? Don't such substances belong to everyone? Should proprietary interests be confined to that which we produce and extended only to some things that occur naturally? Analogies to owning property (Macer, 1991; Merges, 1993) or to mining rights (Cook-Deegan, 1994) have been made both to dismiss and support this question. On one hand, patenting naturally occurring, unassigned human DNA sequences can be viewed as similar to land settlement. For example, during colonial rule, discoverers could claim land as their property. But in later years, policymakers and courts recognized that the indigenous people had claims to the property for reasons of social justice, regardless of the extent of the colonizers' development (Macer, 1991). On the other hand, intellectual property rights to human DNA sequences also can be viewed as similar to most private ownership of property. Tangible private property can have as its physical basis some naturally occurring substance (e.g., minerals), yet this does not preclude private proprietary rights. Minerals can add value to a parcel of land and are sometimes unknown at the time of claim. Why should human DNA sequences be different? That is, the ultimate value of any particular DNA sequence might be ill-defined at the time of the claim, but should proprietary rights be blocked until true value is identified?

From a philosophical standpoint, the question also can be reduced to an analysis of justifying property rights per se. At least since the time of John Locke, philosophers have recognized that the fundamental problem about justifying private property rights is justifying individual rights over collective ownership of substances that might be viewed as, in some sense, the common possession of all of humanity. Many theories have been developed and analyzed (Becker, 1977, Munzer, 1990). In summary:

- Private property rights increase economic efficiency by providing incentives for those who have labored to develop and use what occurs in nature.
- Private property rights emerge out of people's mixing their labor with previous unowned property and making it theirs.
- Private property rights are the just rewards for those who have labored in useful ways.
- Property rights respect those who have labored because the individual labor benefits society collectively.

These arguments can be used, then, to justify private rights to previously uncharacterized, naturally occurring human DNA sequences, even if they have not been manufactured as something new and are society's common possession--just as private ownership has been justified for land or minerals. However, some see an important distinction between rights for human DNA sequences and rights for other private property in naturally occurring substances. Unlike other private property, human DNA sequences in their natural state are internal, rather than external, to us. This difference goes to the heart of concerns about human dignity, which is discussed in a following section.

Defenders of property rights also have been aware that, whatever the justification for private property, there is the problem of the potential harm to everyone who can be excluded from the property by the owner. Locke attempted to deal with this problem by imposing a restriction on the acquisition of private property, the Lockean Proviso, whose fundamental point is ensuring that others not be harmed when private property rights emerge. Nevertheless, of the different types of proprietary protection, the problem might be most acute for intellectual property rights--both if the

rights are in what is newly created, but even more so if the rights are in what has always existed and is merely newly discovered and isolated (Gordon, 1993). One individual argues:

In sum, if there is only one culture (and whether technological or literary culture is at issue, the point is the same), a person who wishes to contribute to it usually is required to use the tools of that culture. Giving first creators ownership over any aspect of the culture, even if that aspect is newly created, may make a later creator less well off than he or she would have been without the new creation. Intellectual products, once they are made public in an interdependent world, change that world. To deal with those changes, users may have need of a freedom inconsistent with first creators' property rights. If they are forbidden to use the creation that was the agent of the change, all they will have to work from will be the now devalued common (Gordon, 1993).

What are the implications of this argument for patents on human DNA sequences? If researchers are excluded from working on certain problems because relevant stretches of DNA have been patented by another party, the granting of that intellectual property right might be viewed as having unfairly harmed the new researchers. In other words, such researchers might have been better off if the discovery of the relevant piece of DNA had not been made and the patent not awarded, since the DNA sequence exists in nature waiting to be identified and freely used. Arguably the difficulties presented by such a scenario are not unique to patents on human DNA sequences. However, some argue that specifically because human DNA sequences are part of society's common heritage, it is morally wrong for the emergence of intellectual property rights on human DNA sequences to impede the work of new researchers.

It might be that the rights of patent holders of human DNA sequences should be limited, with other researchers allowed free use of the substances in their own research. The legal arguments related to this issue, often referred to as the experimental use exception (Eisenberg, 1987), are examined in chapter 3. Briefly, the experimental use doctrine seeks to reconcile the rights of patents with the norms of scientific conduct, i.e., progress in basic research hinges on unimpeded access to past discoveries. The experimental use doctrine, however, can also be defended from a moral perspective; it can serve as part of the justification of the very existence of private property rights in society's common heritage, rather than solely a legal reconciliation between property rights and

scientific interests. In other words, the experimental use doctrine could be viewed as a balance between moral justifications of private property ownership of common heritage and public access to that same heritage.

Overall, an argument can be made that analyzing common heritage issues reveals that merely because human DNA sequences are found in nature as part of a common heritage might not be sufficient to declare that property rights in such substances are immoral (Brody, 1993). It might be, however, that a legitimate system of property rights in human DNA sequences should, from a moral basis, include an experimental use exception. Left unanswered is the issue that human DNA sequences in their natural state are internal, and so bear a special property relation to each individual because of the respect paid to concerns for human dignity. The following section analyzes these issues.

Issues Related to Human Dignity Concerns

Does the special nature of human DNA sequences make the intellectual property protection of them incompatible with human dignity? Four themes underlie this question. First, intellectual property protection of in human DNA sequences is immoral because it is equivalent to ownership of humans. Second, rights to such substances are inappropriate because it is like the ownership of body parts or other things that should not be commercialized. Third, intellectual property protection of human DNA sequences is inappropriate because these substances define human identity. And fourth, patenting human DNA sequences is immoral because it might involve inappropriate modifications in our genetic integrity.

Patenting Human DNA Sequences Versus Humans

The fundamental intuition behind this theme is that any proprietary right in human beings is absolutely immoral. The prohibition against slavery is an aspect of this broader moral intuition. Even

if other living things can be owned and patented, human beings cannot. The U.S. Patent and Trademark Office, however, has no basis to resolve issues based on moral intuition (McCoy, 1992). Prohibiting a claim that includes a human being within its scope, while having a moral basis, also has a constitutional basis (Rivard, 1992).

Because of this constitutional protection, theories of what entities are entitled to such protection have developed. One proposal suggests that protections be confined to members of species whose average mature member has the capacity for self awareness (Rivard, 1992). If applied to the current controversy, there appears to be no moral quandary over intellectual property protection of human DNA sequences, only with only complete human beings. Still, those advocating such a delineation are aware of the difference between proprietary rights in humans versus those for human components. These voices propose that the protection of human dignity requires expansion to include human body components (Brody, 1993).

In fact, such was the approach taken by the Commission of the European Community (EC) in a draft discussion document. The draft concluded that “in the light of the general principle that the ownership of human beings is prohibited, the human body or parts of the human body per se must be excluded from patentability (Commission, 1992; Commission, 1994).” However, “parts of the human body per se” encompasses those “found inside the human body. It is important that this be spelled out so as to remove all possible ambiguity with respect to the position of certain products or parts of the human body which are already covered by patents granted in connection with the development of medicinal products” (Commission, 1992; Commission, 1994).

Examining this language reveals a few contradictions. First, no elaboration is offered on the moral basis for the extension to include human parts. Second, because the basis for the extension is undefined, it is difficult to ascertain whether extending the prohibition to encompass body parts as long as they are within humans is morally justified. Finally, it does not extend to include a prohibition on patenting ex vivo DNA sequences--a stance clearly taken elsewhere by the EC (box 4-B).

Noncommercialization

This theme posits that the monopoly rights to make, use, or sell human DNA compositions, like the sale of certain body parts (e.g., organs for transplantation), is an inappropriate commodification that weakens human dignity. That is, protecting human dignity requires restricting market freedom by treating some things as noncommodities that cannot be owned and sold.

This argument differs from the one related to owning human beings. As just described, that argument centers on a moral prohibition against owning and selling a person, without an elaboration of the moral basis for extending the prohibition to include human parts. In contrast, this argument focuses on a widely accepted prohibition against the ownership and sale of certain human parts (OTA, 1987). It provides a more secure foundation for a moral opposition to the ownership and sale of human DNA sequences made possible by intellectual property protection.

A history of philosophical thinking stresses the moral need to protect certain items from being treated as commodities (Titmus, 1971; Walzer, 1983; Radin, 1986, 1987, 1989). One of the earliest applications involved the blood supply¹ (Titmus, 1971), where the argument was made that scientific advances have increased the social need for altruism and gift relationships and that refusing to pay for blood to be used in transfusions was an appropriate way to meet that need. Another philosopher drew a list of fourteen blocked transactions of things that money cannot buy, although body parts was not among them (Walzer, 1983).

It would be easier to assess philosophical issues related to commercialization of human DNA sequences if a good general theory existed about what sorts of things should or should not be treated as commodities. For example, while some argue in favor of recognizing organs as personal property

¹In the United States, individuals are sometimes paid for the collection of blood (or semen), but such payment has been judged, from a legal perspective, to be for services rendered, not for the blood as a commodity (OTA, 1987).

that can be sold (Andrews, 1986; Scott, 1981)), a number of reasons have been articulated on moral oppositions to commercializing blood for transfusion or kidneys for transplantation (Anderson, 1990; Neslon 1991; Andre, 1992). Despite such attempts, which could apply to the commodification of human DNA sequences, there is a difference between those cases and the commercialization of human DNA sequences.

In the case of kidneys, identifiable human beings would, for a price, allow bodily material to be taken from them to be incorporated into another body. An analogous process for human DNA sequences would be taking genetic material from one individual and incorporating it into the body of another. This is not, of course, what is involved in the process that would be protected and commercialized by allowing patents on human DNA sequences like ESTs; sequence donors are not present per se, even with gene therapy. Rather, some cells are taken from donor tissue or fluids, and then used to isolate and sequence the human DNA. The sequences are then produced for commercialization through molecular biological techniques. That is, blood or kidneys are useful without added effort, whereas commercialization of human DNA needs both financial and intellectual investment. This subtle difference affects the moral arguments.

Claims are often made that those who would sell kidneys are poor people being exploited by the affluent, and that their human dignity is impaired by this exploitation (Andre, 1992; Brody, 1994). Yet this point does not pertain to the commercialization of human DNA sequences via patenting, since the substances to be sold are produced, not purchased. Currently, commercializing human DNA sequences does not involve giving up human biological material because of poverty; the vast majority of material involved is long-abandoned tissues or fluids. Even in rare instances when material from a single individual is involved (OTA, 1987), most argue that, ethically and legally, human dignity is not impaired as long as the donor knows that material which would otherwise be discarded will be used for scientific, and potentially marketable, purposes (John Moore, 1988). Additionally, it has been suggested that allowing a market to develop in human biological material undercuts society's ability to live in a community of caring and sharing individuals who donate, rather than sell, what others

desperately need (Andre, 1992; OTA 1987; Murray, 1986; Wartofsky, 1981). Again, this point seems not to be directly relevant to the commercialization of human DNA sequences through patenting, since the material to be sold would not otherwise be donated by caring and sharing individuals.

Attempts have been made to identify some principle, other than a sui generis moral principle--e.g., it is just wrong to sell any human biological material--that could be grounded in considerations such as the need to preserve human dignity and could serve as the basis for a moral objection to the sale of human biological material. One attempt offered is that it is wrong to sell something "intimate" (Nelson, 1991). Another possible argument posits that it is wrong to commercialize something with which individuality and personhood are intertwined (Radin, 1991). This theme appears to provide a moral objection to the commercialization of human DNA sequences, since they do seem to be connected with human identity and, in part, with personal identity. Furthermore, it leads to the third line of objection: It is wrong to commercialize human DNA sequences because this undercuts human dignity by commodifying the very thing that defines, to some extent, personal identity--even if limited to DNA sequence variation for the purpose of forensic identification or tissue typing for transplantation.

Human Identity

The third moral objection can be formalized as follows. First, it is wrong to commodify that which defines human and personal identity because doing so impairs human dignity. Second, human DNA sequences help define human and personal identity. Third, patenting human DNA sequences involves patenting that which helps define human and personal identity. Therefore, patenting human DNA sequences is morally wrong because it commodifies that which helps define human and personal identity.

As just noted, a moral objection could be raised that it is wrong to commodify something intimately connected with human and personal identity (Nelson, 1991; Radin, 1991; Brody, 1993). The second premise is also true, but only partially: It is important to note that a reductionist view that human DNA sequences are solely responsible for personal identity is false, since no acknowledgement of environmental or cognitive influences is made. Additionally, the human genome shares significant homology with animal genome--i.e., most human DNA sequences are not, in fact, truly unique to humans. Still, despite those caveats, the third assertion logically follows, as does the conclusion. Thus, it appears that one moral challenge to patenting human DNA sequences might be grounded in concerns about human dignity and the role of genetic make-up in human and personal identity.

Objections to this argument can be raised from several perspectives. Foremost: The extent to which human DNA sequences are linked to self identity is not unequivocal; being human is not simply a matter of having a certain DNA sequence (Hubbard, 1993; Lewontin, 1992). Moreover, the history of philosophical reflection on personal identity reveals that two fundamental approaches dominate traditional discussions (Perry, 1975). One approach is the psychological approach, wherein psychological continuity defines personal identity, with special emphasis on memory connecting the present self with the past self and intentions connecting the present self with the future self (Locke, 1690). Under this approach, personal identity is entirely independent of any bodily factors. Based on this premise, then, human DNA sequences, as part of the body, would not be factors in defining individual personal identity, and hence the original moral objection becomes void. A second adopts a bodily approach to human and personal identity, wherein personal identity is defined in terms of bodily continuity--i.e., defined in terms of a body occupying a spatio-temporally continuous set of locations (Priestly, 1777). Yet, while this approach makes personal identity dependent on bodily factors, the factors in question are not genetic. Thus, applying traditional philosophical reflection, the notion that human DNA sequences help define personal identity is ambiguous.

On the other hand, some contemporary thinking about the philosophical underpinnings of personal identity might offer support. One, dubbed the Zygotic Principle (Williams, 1990), sees

origins as crucial to the identity of any living thing and the union of two gametes carrying a full set of specific genetic information as crucial to the identity of a human being. The second derives from arguments of the abortion controversy--i.e., some assert that a human being comes into existence at the moment of conception precisely because that which defines identity--the unique, never to be repeated combination of genetic material--comes into existence at that moment (Ramsey, 1970). Thus, although highly controversial, these two approaches offer a basis for defending the assertion that human DNA sequences are, at some level, inseparable from both human and self identity.

On the other hand, central to both lines of defense is that full sets of genes are explicitly involved and are what purports to constitute identity. But as a practical matter, the patenting of human DNA sequences does not involve patenting a full set of genes; what is patented in each case is a specific gene or sequence that is not unique to any human being and is often not even a uniquely human sequence. Thus, the third premise--patenting human DNA sequences involves patenting that which helps defines human identity--does not immediately follow, except for an application to patent an entire set of genes, which has never been proposed (but for which clear moral objections can be raised because of human dignity considerations such as slavery). In contrast, there appears to be no moral imperative to reject the patenting of a specific human DNA sequence because it defines human or personal identity.

Preserving Human Genetic Integrity

The last of the central issues to be analyzed is the suggestion that respecting human dignity involves preserving human genetic integrity, and that this requires a ban on the patenting of human DNA sequences that might be altered once they were patented.

There is a range of possible reasons why individuals might believe in preserving human genetic integrity. Their belief might be part of a metaphysical or religious commitment to preserving genetic integrity in general (World Council, 1992); what is unclear is whether such a belief is compatible with

a modern evolutionary understanding of the genetics of species. A likely possibility, however, draws its roots from reflections on the history of the eugenics movement.

The desire by adherents of that movement to “improve” human beings stemmed from their failure to respect human dignity because they perceived individuals as “flawed.” Thus, an objection might be made that genetic manipulations of human DNA sequences will reinforce eugenic concepts and renew a lack of respect for the dignity of all humans. Based on this argument, patenting human DNA sequences should be banned to eliminate the possibility of commercializing these genetic modifications as a positive good. Such a ban would then quash the likelihood of increasing a disregard for human dignity.

In fact, concerns about eugenics influenced the EC’s debate (Commission, 1993; Commission, 1994). “Processes for modifying the genetic identity of the human body for a nontherapeutic purpose, which is contrary to the dignity of man, is [sic] not patentable” (Commission, 1992; Commission, 1994). The EC proposed directive intensely argues the need to preserve human dignity against eugenic tendencies, but also recognizes that alternatives to a total ban on the patenting of human DNA sequences exist. The boundary the EC proposed directive adopts is a selective ban that prohibits patenting substances that do not conform with respect for human dignity. Theoretically, society may reap the benefits of intellectual property protection for human DNA sequences, while protecting against inappropriate eugenic tendencies.

On the other hand, the EC proposal would ban the patenting of certain processes for producing inappropriate genetic modifications. A different approach would be to ban the patenting of the inappropriate modifications themselves, in part because they deserve direct discouragement but primarily because the processes for making the modifications are likely to be the same whether or not the modifications are appropriate. Additionally, the ban on patenting in the proposal applies only to nontherapeutic modifications that are also incompatible with the dignity of human beings, but an EC explanatory memorandum that accompanies the proposal suggests that only modifications that are

both therapeutic and compatible with the dignity of human beings should be allowed, (European Community, 1993), which is a stronger requirement. Finally, what constitutes “therapeutic” and “contrary to the dignity of man” go undefined.

Thus, the issue of respect for human dignity offers some support for a moral objection against patenting of human DNA sequences. As well, moral arguments support a ban on patenting an entire set of human genes and some restrictions against patenting human DNA sequences for eugenic purposes.

Issues Related to Just Order Concerns

A third central moral issue involves questions of equity and justice. Although such questions apply both to inequities within a country and among nations, concerns about biological research, intellectual property, and a just order largely have focused on the international context; they are not novel. In fact, misgivings are not limited to perceived injustices related to the economic gap between developed and developing nations, but that intellectual property rights in biotechnology will greatly exacerbate the disparity (Dembo, 1985; Macer, 1991; Curien, 1991); such concerns led to provisions in the international Convention on Biological Diversity that facilitate the transfer of biotechnology from industrialized countries to developing countries on favorable terms (Burk, 1993; box 4-F). On the other hand, neither industrialized nor developing nations will benefit from genetic discoveries unless incentives exist, such as those provided by patents, to develop commercial products (Healy, 1992). The argument also is made that patents are an inappropriate mechanism for asset or income distribution (Hensley, 1993). Still, do patents result in too much of the benefits going to industrialized countries and too little going to developing countries?

Two different approaches are relevant to concerns about a just international order. The first asks whether the patents on human DNA sequences lead to unjust (Dembo, 1985) purchases by citizens of developing countries of the patented products from corporations centered in the

industrialized world. The second asks more globally whether patents, including those on human DNA sequences, contribute to an unjust international distribution of wealth.

On the one hand, people in developing countries are free to purchase, or not purchase, newly patented products, and they will buy them only if they judge that the products are worth the cost. Why such transactions are morally unfair is not clear--unless there is a general objection to the fairness of exchanges in the free market as a way of allocating benefits between buyers and sellers, or some reason why this case is special. On the other hand, people in developing countries, while theoretically free to make purchasing decisions, are likely constrained from doing so due to lack of money. Such a limitation could be viewed as unjust for patented products comprised of material viewed as part of humanity's common heritage.

Additionally, patented products involving human DNA sequences might be viewed by some as a special case. First, the vast majority of products derived from human DNA sequence patents are, and will continue to be, for therapeutic or diagnostic purposes. Since many countries either prohibit or decline to enforce patents on such items, based on an underlying assumption that deriving profit from vital substances is immoral, human DNA sequence patents, with clear links to health purposes, might be viewed as immoral. And second, if the substances are deemed part of society's common heritage, then it might be viewed as morally wrong that individuals in developing nations must purchase the patented products--i.e., is it just that some countries can own, through patents, substances that are found in all of humanity? Does this mean that the intellectual property rights in question are inappropriate? Does this mean that this case is special and that the exchanges in question, while free, are still unfair?

This argument rests on the assumption that property rights in human DNA sequences are inappropriate because the material is part of a common heritage. As examined earlier in this chapter, however, moral arguments related to common heritage concerns are equivocal. Hence, the basis for

claiming that the free exchanges just mentioned are morally unfair to consumers in developing countries is also murky.

Nevertheless, the question remains of the general justice, or injustice, of the current distribution of wealth between industrialized versus developing nations and the possible contribution of intellectual property rights in human DNA sequences to amplify such injustices. To adequately analyze this assertion would require developing a substantive theory of a just international order--a topic beyond the scope of this report. It would also require an empirical analysis of the extent to which patent rights, generally--and those for human DNA sequences, specifically--might contribute to economic disparity; also beyond the scope of this report. In any case, it would seem that, from a policy perspective, the focus should not be on the potential impact of human DNA patents, but on addressing the issue of international injustices in ways that are more important and could have a more substantial impact.

SUMMARY AND CONCLUSIONS

Today's debate about ethical considerations of patenting human DNA sequences has roots in similar discussions about patenting microorganisms and animals, but takes a different form because it involves human biological material. In general, three moral questions lie at the heart of the controversy. First, is it appropriate to patent human DNA sequences if they are viewed as part of humanity's common heritage and so should be in society's custody? Second, is patenting human DNA sequences compatible with respect for the dignity of human beings and human life? And third, will patents unfairly affect research and commercial efforts in developing nations?

The first question centers on the belief of some that governments should prohibit patents on things that occur in nature because such substances belong to society's common heritage. The second query focuses on four notions--that patenting human DNA sequences is tantamount to a property right in human beings; that monopoly rights to make, use, or sell human DNA compositions is an

inappropriate commercialization that weakens human dignity; that patenting human DNA sequences is morally wrong because it commercializes that which helps define human and personal identity; and that respecting human dignity involves preserving human genetic integrity by prohibiting manipulation and modification of human DNA sequences. Embedded in the third question are notions of equity and justice--that intellectual property rights in biotechnology exacerbate economic disparities within and among nations.

Overall, a philosophical analysis of common heritage issues reveals that merely because human DNA sequences are found in nature as part of a common heritage might not be sufficient to prohibit intellectual property rights. For example, tangible property rights can be claimed to naturally occurring substances such as minerals. Still, common heritage concerns might justify, on a moral basis, a system of property rights in human DNA sequences that includes an experimental use exception.

With respect to human dignity concerns, there appears to be no moral imperative to reject the patenting of a specific human DNA sequence because it defines personal or human identity. A reductionist view that human DNA sequences are solely responsible for personal identity is false, since such a perspective ignores environmental or cognitive influences: Humans are not just walking DNA molecules. Moreover, the human genome shares significant similarities with animal, plant, and microbial genomes--i.e., most human DNA sequences are not unique to humans as a species, and thus do not define human identity. On the other hand, morally based objections against an application to patent an entire set of human genes can be characterized. As well, moral arguments against patenting human DNA sequences for eugenic purposes exist.

Finally, just order concerns about patents on human DNA sequences might be viewed as unjust based on a general objection to the fairness of exchanges in the free market. On the other hand, considerations about equity and justice largely trace back to assumptions about human DNA sequences as part of a common heritage. Yet, moral arguments in this area are equivocal. Moreover,

policymakers seemingly can approach the issue of economic disparity--and achieve a more substantial impact--through means other than analyzing the potential impact of human DNA patents.

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Box 4-A--Historical Perspective on Ethical Considerations of Genetics

Although the origins of contemporary public discourse on ethical dilemmas associated with the commercialization of biological information trace back to the U.S. Supreme Court's 1980 decision in Diamond v. Chakrabarty, discussions about the ethical implications of genetic information are much older. Since rediscovery of Mendel's laws of heredity at the turn of the century, society has debated strategies for prevention based on new genetic discoveries, as well as the merits of intervention to improve the gene pool (Allen, 1989; Cook-Deegan, 1994a,b; Kevles, 1986; Haller, 1984; Fausto-Sterling, 1985, 1992; Mendelsohn and Elkana, 1981).

Eugenics, a social and intellectual movement that advocated initiatives ranging from sterilization to immigration restriction, gained favor among late 19th and early 20th century Americans and Europeans who argued that particular races and ethnic groups were inferior to white, Anglo-Saxon Protestants. Originally coined in 1883 by Sir Francis Galton, a cousin of Charles Darwin, eugenics means "noble birth" (Kevles, 1986). Genetics, in the hands of eugenicists, would come to be used to justify Nazi experiments and genocide and the Tuskegee syphilis study (Jones, 1981)--all in the name of prevention. The collective memory of these episodes has greatly influenced contemporary public reactions to the issue of patenting human DNA sequences (Hubbard, 1993; Kevles, 1993; Draper, 1993; Langfelder, 1993; Draper, 1991). In fact, the prospect of widespread patenting of ESTs furthered calls for ethical standards among proponents and detractors of the Human Genome Project (Hood, 1993; Larson, 1993; Nelkin, 1989; Rothman, 1991; Mayr, 1982)

That genetics gained a broader scientific legitimacy in America through the popularization of the eugenics movement has only exacerbated debates on at least three questions related to patenting human DNA sequences. First, how will these new technologies differentially affect social groups? Second, how has genetic information been misused in the past to stigmatize, marginalize, and discriminate against individuals and groups? And finally, can public education and discourse on ethical considerations address fears that ownership of human DNA incites?

During the 1920s and 1930s, public policies rooted in eugenics expanded as genetic misinformation was used increasingly to marginalize and discriminate against various social groups (Hubbard, 1993; Duster, 1990; Kevles, 1992). Hereditarianism pervaded American society--e.g., attributing crime and poverty as distinct problems rooted in genetic makeup--a theme that has resurfaced (Walters, 1993). Advocates of eugenics maintained that the best way to prevent rising incidence from these problems in Blacks and the ethnic immigrant poor was to intervene early (Gould, 1981) by improving the gene pool through selective breeding, while simultaneously preventing deleterious traits through sterilization and immigration restrictions (Kevles, 1985; Reilly, 1991; Cook-Deegan, 1994a,b).

A coalition of mid-20th century anthropologists, biologists, and social scientists generally helped undermine the popularity of eugenics following discoveries of Nazi abuses. Increasingly, this coalition and an emerging group of empirical sociologists rejected earlier declarations of genetic reductionism, by pointing to the influence of culture in shaping what earlier had been ascribed to biological and behavioral characteristics of race, gender, and class. By the mid-1950s, population geneticists also would underscore the influence of polygenic inheritance as a key factor in the expression of human traits (Mayr, 1982; Brock, 1992). Moreover, the discovery of interracial and intraracial genetic variation further highlighted the fallacy of homogeneous social groups espoused in earlier eugenic arguments.

Still, despite the growing attack on the misuse of genetic information during the last half century, advocates of stricter ethics standards in the current debate on patenting have highlighted how recent episodes attest to the need for better supervision in the application of scientific authority (Lewontin, 1974; OTA, 1993). It was not until 1981 that the U.S. Air Force Academy rescinded its policy of excluding Blacks with sickle cell trait from pilot training, based on the erroneous belief that a low-oxygen environment (e.g., high-altitude exertion, flights, or deep-water activity) would cause a carrier to undergo a sickling experience (Duster, 1990). One focus of current concern is that genetic

discrimination will accelerate as insurance companies, for example, obtain new genetic data (Draper, 1993; Jaeger, 1993; Hubbard, 1993).

The historical resonance of eugenic ideas in debates about the Human Genome Project presents obvious dilemmas for scientists, health care professionals, policymakers, and the public. It is a debate that the NIH applications for patents on ESTs has sharpened, especially in the moral realm.

SOURCE: Office of Technology Assessment, 1994.

Box 4-B--The Human Genome Diversity Project

While the 15-year, \$3 billion Human Genome Project seeks to map and sequence a Caucasian “reference” genome (Botstein, 1980), the Human Genome Diversity Project was proposed in 1991 to explore variation in human genomes, both normal variation and variation responsible for inherited disease (Bowcock, 1991; Cavalli-Sforza, 1991; Diamond, 1991; Roberts, 1991b). Project supporters seek to retrieve blood samples and examine the DNA of 20 to 25 unrelated individuals from each of 400 to 500 populations of historical interest around the globe (Rensberger, 1993), many of which literally face extinction. By revealing as much as possible about the current state of genetic diversity among humans, they aim to address four questions: How has human phenotypic variation evolved? To what extent can variation in disease risk among modern populations be explained by human genetic diversity? How are human societies structured? Where did modern humans come from (HGDP, 1992a; McKusick, 1992)? The project could also elucidate why some populations are more, or less, susceptible to certain diseases (King, 1993).

Scientists proposing the Human Genome Diversity Project estimate its cost at \$23-25 million over five years (Ross, 1993). Federal funding might derive from three U.S. sources--singly or in collaboration: the National Science Foundation (NSF) (which supports anthropology research) and the National Institutes of Health (NIH) and the Department of Energy (DOE) (which together fund the Human Genome Project). Neither NIH nor DOE has included funding for the Human Genome Diversity Project in its current 5-year plans for the Human Genome Project (Collins, 1993; Galas, 1993), although all agencies contributed funds for planning workshops held in 1992 and 1993 (Greely, 1993; HGDP, 1992a, HGDP 1992b; Roberts, 1992c; Roberts, 1993).

Several technical aspects of the proposed Human Genome Diversity Project remain to be settled. For example, researchers must finalize the populations to be sampled and define the minimum set of genetic markers to be analyzed (Cavalli-Sforza, 1993). The proposed project also faces several ethical, cultural, and social issues. In particular, since genetic differences are the proposed project’s focus, concerns are raised about information being used to support notions of superiority of one group

over another and reinforce conventional views of race and ethnicity (Greely, 1993; Lewin, 1993; Rensburger, 1993). Concerns are also raised about potential conflicts between U.S. regulations governing human subjects research and the practices, values, or beliefs in other societies (Greely, 1993; Lee, 1993; Nishimi, 1993). Finally, the Human Genome Diversity Project raises questions related to intellectual property rights for individuals, researchers, and nations--a particular concern since many of the populations proposed for sample collection live in developing nations that have already expressed concerns about the general issues surrounding DNA patents (McKusick, 1992). The interplay of the intended availability of resources, their potential commercial value, and the intellectual property rights of all parties involved remains to be seen.

SOURCE: Office of Technology Assessment, 1994.

Box 4-C--European Statements on the Morality of Human DNA Patents

Although questions about ethical considerations of patenting microorganisms, plants, animals, and human DNA sequences have been raised universally, they have been articulated most often in policy statements or legislation from outside the United States (Nature, 1993a, 1993b; L'Express, 1994). For example, European intellectual property law related to biotechnology specifically takes note of a range of ethical concerns--in part as a reaction to the eugenics component of the Nazi program and in part because of biodiversity and environmental concerns. One reason intellectual property protection related to biotechnology has lagged in the European Community is because of ethical questions (Maher, 1992).

In November 1988, the Commission of the European Community first examined a directive on the legal protection of biotechnological inventions. Serious ethical questions were raised during discussions in the European Parliament in 1992, which led to an amended proposal in December 1992 and adoption of a directive in February 1994 (Commission, 1994). Official commentary appended to the proposal offered:

It goes without saying that, if the applicant simply wishes to patent a mere part of the "human body" per se, e.g., a human gene neither the function of which nor the protein for which it codes is known, exclusion from patentability would apply.

The directive is not based on the disadvantages to science of early patenting. Instead, it is part of an article designed to deal with moral qualms about patenting human bodies or their parts. Europeans consistently have raised moral concerns about patenting human bodies and their parts, and so propose that DNA sequences, partial or complete, with unknown function should not be patented (Commission, 1993).

Nongovernmental organizations in Europe also have raised ethical questions about intellectual property protection of human DNA sequences. For example, the World Medical Association issued a blanket opposition to patenting human DNA sequences in its Declaration on the Human Genome

Project adopted in Marbella, Spain in September 1992 (World Medical Association, 1993). The association believes no patents should be granted for “the human genome or parts of it, because such information “should be general property and should not be used for business aims.” Legislation introduced in the French Parliament also proposes a ban of similar scope (Herman, 1992; L’Express, 1994), although the bill is now being reconsidered by a new French minister for research (Patel, 1993).

SOURCE: Office of Technology Assessment, 1994.

Box 4-E--Anthropologic and Ethnographic Considerations

In considering concerns for human dignity and common heritage, anthropologists and ethnobiologists express a range of opinion for and against intellectual property protection of DNA (Attali, 1994; Bono, 1993; Posey, 1990; Brush, 1993), with a focus on how cultural and social contexts are important influences on the trend toward commercialization of biological information and substances. In particular, how has this trend reflected shifts in prior practices regarding respect for human dignity and a common heritage? And, how would different social groups profit from further intellectual property protection of biological materials and information--in particular, DNA?

The increased proprietary protection of biologic information--made apparent in applications on plants, medicinal agents, and other naturally occurring substances--has stemmed from biotechnology's challenge to prior beliefs that some knowledge was the province of the entire society (Brush, 1993). Although historians have described a similar phenomenon during the early 20th century, the popularity and widespread support for biotechnology have fueled contemporary dilemmas about the use of, or constraints on, intellectual property protection of materials of nature (Kevles, 1993). For example, anthropologists have described tensions that have arisen from the adoption of herbal remedies in industrialized countries, where rights are granted to such knowledge exclusive of the local context in which the biological material or information was first disseminated (Posey, 1990; Spuhler, 1991).

Additionally, many argue that the fact that patents in some countries are issued for biological products produced in another also challenges notions of human dignity--especially as ethnobiologists and ethnographers find that patterns of exploitation often result from the importation and protection of biologic knowledge and substances from one culture to another (Brush, 1993; Kidd, 1993; Allen, 1989). In this context, some experts argue that the prospect of patents on human DNA sequences will fuel a fear that human dignity will be undercut as people commercialize and market things they believe had value as part of a common heritage. In particular, anthropologists have long recognized and emphasized that biological knowledge is among the most important type of information possessed by

any culture. As such, many propose that the inestimable value of biologic knowledge be treated as a common heritage to be shared for the benefit of all humanity, instead of as a monopoly for private gain (Brush, 1993).

Even with the withdrawal of NIH's patent application, moral arguments for and against intellectual property protection for human biological material will continue to reflect evolving concepts of common heritage and human dignity within the international scientific and lay communities (Wade, 1994). For example, current discussions related to the Human Genome Diversity Project and ongoing patent applications on cell lines obtained among private researchers prove that common heritage and human dignity claims will remain enduring parts of the moral dilemmas raised by ownership, management, and intellectual property protection of biological material. International controversy about the ethics of patenting a cell line from an indigenous population in a developing country recently forced a Federal agency to withdraw its application (geneWATCH, 1994). As the Human Genome Project and Human Genome Diversity Project move forward, intellectual property considerations will continue to present moral and ethical problems for anthropologists and ethnographers interested in the cultural and social meaning of new scientific practices (Bono, 1993; Spuhler, 1991; Allen, 1989).

SOURCE: Office of Technology Assessment, 1994.

Box 4-D--Ethical Arguments Raised by Patenting Animals

In examining the ethical implications of patenting animals, OTA discussed arguments for and against in a 1989 report (OTA, 1989). The following summarizes some of these arguments,* since similar points are raised in the context of human genome patents.

Arguments For

- Patent law regulates inventiveness, not commercial uses, and the U.S. Patent and Trademark Office is ill-equipped to make ethical determinations on the possible uses of the more than 3 million patents it has granted: The patent statute, though detailed in procedural requirements regarding the application, issuance, maintenance, and reexamination of a patent, is silent on subsequent use or commercial application of a patented invention. The lone statutory exception is the Inventions Secrecy Act (36 U.S.C. 181-188), which allows the withholding of patents that are deemed to be detrimental to national security. The only other way to stop issuance of a patent on public policy grounds is to show that the invention has no possible use. In one case, a court determined that a drug had no utility because “of extreme toxicity to the point of immediate death under all conditions of its sole contemplated use” (Application of Anthony, 1969). Historically, limited court rulings (mainly involving patents on gambling devices) suggest that patents can be denied only if the invention has absolutely no other use than an illegal or immoral one--a standard extremely difficult to meet (Chicago, 1941; Koppe, 1929).
- Such patents promote useful consequences: Consequentialist reasoning--i.e., defending social institutions on the grounds that they lead to desirable consequences--favoring patents on life forms posits that they increase the incentives for inventors to develop useful inventions; are necessary for the United States to compete in an international marketplace; are preferable to trade secrets that hinder free exchange of

scientific knowledge; and outweigh possible harms of, in the case of animal patents, animal suffering, hardship for small farmers, and reduction in genetic diversity.

- Patenting rewards innovation and entrepreneurship: another moral justification for patents on microorganisms, plants, animals, or human DNA is that inventors are entitled to such patents as an acknowledgment of their efforts--i.e., that patents rights are a reward to scientists for the fruits of their labor because that intellectual labor is for the promotion of science (Walters, 1987).

Arguments Against

- Metaphysical and theological concerns about the fundamental nature of reality: Patenting microorganisms, plants, animals, or their components raises questions about the meaning of and relations among living creatures and the world they inhabit. Allowing such patents rests upon a specific, highly reductive conception of life that removes any distinction between living and nonliving matter (World Council, 1982). Additionally, combining human genetic information with animals' or microorganisms', the results of which can be patented, raises unique moral, ethical, and theological questions, such as the sanctity of human worth (Regan, 1983); recombinant DNA technology breaks down barriers between humans and other life forms, yet the sanctity of human worth is a fundamental moral principle of society. Finally, the theme of stewardship over nature has been raised--i.e, the importance of responsibility toward nature and the need to preserve and protect species integrity (Granberg-Michaelson, 1987; Norton, 1987; Passmore, 1974; Rollin, 1981).
- International opposition: Patenting animals must be morally wrong because so many countries have explicitly banned this practice. Further, it is inappropriate because of potential adverse economic implications for developing countries. This latter argument has both a consequentialist component (patenting and the biotechnological innovation

it encourages will lead to bad results for underdeveloped and developing nations) and an equity component (it is unfair for developed countries to exploit less developed countries through patents derived through biotechnology).

*Several ethical issues were specific to animal patents, e.g., patenting involves inappropriate treatment of animals, promotes environmentally unsound policies, and produces excessive burdens on American agriculture.

SOURCE: Office of Technology Assessment, 1994, based on U.S. Congress, Office of Technology Assessment, New Developments in Biotechnology: Patenting Life, OTA-BA-370 (U. S. Government Printing Office, April 1990).

Box 4-F--International Intellectual Property Agreements for Novel Biologics

While questions related to a just international order focus on intellectual property protection on human biological material generally, special concerns also have been raised about the potential exploitation of genetic material from indigenous populations (Roberts, 1991b; 1993). On the other hand, intellectual property agreements for novel plant, microbial, and animal biologics derived from species collected in less developed Nations could prove instructive.

Increasingly, academia and industry recognize the importance of biodiversity to the development of new products, especially in the medical arena. Currently, more than 200 companies and research organizations screen plants and animals for medicinal properties (Atz, 1993; Technology Management Group, 1988). Many insist, however, that the patent laws of the United States and other industrialized countries fail to protect adequately the interests of the nations from which most screened species come. Moreover, since the majority of potentially interesting species are found in developing countries (Atz, 1993), these voices express concern that a developing nation's desire for economic development of its natural resources frequently comes at the expense of ecological and cultural diversity of indigenous peoples.

In response to concerns raised by the commercialization of indigenous plant and animal species from lesser developed countries, a number of parties have developed arrangements intended to reduce potential harm for indigenous peoples and environments, while allowing companies to screen and identify potentially novel therapeutics for which they might seek intellectual property protection (NIH Record, 1994; NIH, 1993; Axt, 1993). For example, NIH's John E. Fogarty International Center for Advanced Study in the Health Sciences has coordinated discussion on balancing drug development, biological diversity, economic growth, and intellectual property rights (Schweitzer, 1991). The Fogarty Center also administers the International Cooperative Biodiversity Groups (ICBG) program, sponsored jointly by NIH, the National Science Foundation, and the Agency for International Development. A primary goal of ICBG is to preserve a sense of mutual benefit in the

commercialization of biologic resources (NIH, 1992). Support for ICBG will total approximately \$2.5 million per year over the next five years, and in December 1993, ICBG granted its first five awards for projects that facilitate biodiversity conservation in the course of research to identify new drugs from the world's natural resources. As part of the program, intellectual property agreements have been negotiated so that income from potential discoveries shall be equitably shared with the local communities and indigenous peoples involved (NIH, 1993).

In a separate initiative, the National Cancer Institute (NCI), under its Developmental Therapeutics Program, has developed a model agreement to govern the collection, development, intellectual property rights, and income sharing of investigations involving natural products as potential sources of novel anticancer and AIDS-antiviral therapeutics (NCI, 199X). In the private sector, Merck & Co., Inc. and a Costa Rican biological research organization, INBio, have an agreement whereby INBio supplies samples in exchange for an up-front payment and a portion of royalties should marketable products be developed (Atz, 1993).

SOURCE: Office of Technology Assessment, 1994.

Table 4-1--Comparison of the Controversies Surrounding Animal Versus Human DNA Patents

Patents on transonic animals	Patents on human DNA sequences or genes
May lead to animal suffering	--
May harm family farms	--
May lead to adverse environmental impacts	--
May lead to international injustices	May lead to international injustices
May lead to violations of genetic integrity	May lead to violations of genetic integrity
May lead to a devaluation of life	May lead to a devaluation of human dignity
--	Fails to respect the common heritage of humanity

SOURCE: Office of Technology Assessment, 1994, based on B.A. Brody, "Ethical Considerations in Patenting Human DNA Sequences," contract document prepared for the U.S. Congress, Office of Technology Assessment, 1993; and R. Dresser, "Ethical and Legal Issues in Patenting New Animal Life," *Jurimetrics Journal* 28: 399-435, 1988.

CHAPTER 5

RESEARCH AND DEVELOPMENT IMPLICATIONS

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No one should approach the temple of science with the soul of a money changer.

Thomas Browne (1605-1682)
English physician and writer

The United States is not the only country with a Human Genome Project. Western European nations and Japan have extensive genome research efforts, and the U.S. project also involves laboratories and investigators from essentially any country conducting biomedical research (table 5-1). Hence, both our patent policies and technology transfer practices related to genome research are of significant interest to other countries.

As described previously, when the National Institutes of Health (NIH) announced it had filed patent applications on thousands of expressed sequence tags (ESTs), scientific reaction was swift and largely negative--perhaps no where more uniformly so than in Europe. The United Kingdom (Owen, 1992) and France (Curien, 1992; Kahn, 1992) publicly expressed opposition to the NIH applications, and the 12 member nations of the European Community also unanimously expressed concern (Fayl, 1992). The United Kingdom Medical Research Council (MRC) was accumulated its own, new cDNA sequences at the time of the NIH decision to patent. Thought the MRC intended to place its sequences directly into a database, the NIH decision spurred the MRC to withhold the information from the databases until the MRC reache a decision to file its own patents. Despite its reservations, the MRC filed its own British patents to ensure a place in the debate and provide a defensive position for the United Kingdom (Hudson, 1992; Rees, 1994). And, although the MRC (###MRC, 1993), and more recently the NIH (###Nature, 1994) withdrew their applications, the filings highlighted research and development issues central to the future potential of the Human Genome Project.

Because the Human Genome Project's reach is broad, both domestic and international research collaboration are essential to its success. Yet, few data have been collected and analyzed about how U.S. policies--as well as those of other countries--might affect such cooperation. Does today's unprecedented interest in pursuing patents on genome research--or other biomedical research--stifle research, foster secrecy, or inhibit cooperation and interchange? Or, is technology transfer viewed as

success for a scientist and his or her institution--necessary for generating income, providing unique opportunities, promoting collaboration, and accelerating research discoveries? How do molecular biologists view these issues compared to perspectives of biotechnology companies?

To place today's debates in context, this chapter first reviews the history of university patenting on the dissemination and use of scientific research. Based on OTA's survey of a sample of U.S. molecular biologists who receive research funding from NIH and on discussions at an OTA workshop of international genome scientists, the chapter analyzes researchers' attitudes toward patents and technology transfer, as well as their perceptions of the impacts of these issues on their research practices. Finally, the chapter explores industry's perspectives on commercialization of the Human Genome Project.

HISTORICAL PERSPECTIVE

Seeking patents on the results of faculty research has a long history in American academia. Since at least the turn of the century, the argument has been made that such patents serve the university's interest by producing income that could be plowed back into laboratories. The point also was made that, through patents, universities could control the development, quality, availability and profitability of inventions (Apple, 1989; Bliss, 1982; Cameron, 1982; Kevles, 1993; Weiner, 1987)--a theme echoed recently by the researcher who has identified a genetic pattern possibly associated with male sexual orientation (WP, 1994). Still, fiscal considerations dominated.

During the 1930s depression, universities increasingly sought patents to translate the products of their laboratories into funds for further research. By the late 1930s, some two dozen--and by the late 1940s some 200--universities and colleges had established procedures or agencies for patenting faculty inventions (Gray, 1936; Potter, 1940; Weiner, 1986). Still, many researchers held that university-based science should be unadulterated by commercial considerations. Of primary concern was the belief that industrial commitments would foster secretiveness, which in turn would undermine

the open exchange of information and research reagents that are essential requirements of scientific progress (American Association for the Advancement of Science, 1934; Gray, 1936; Weiner, 1987).

Academic researchers' resistance to patenting was particularly strong in the biomedical sector, where it was commonly assumed that discoveries useful to health and medicine should be made freely available for public benefit. For example, University of Toronto scientists who were responsible for the purification of insulin excluded themselves from shares in revenue from the insulin patent, assigning their rights to the University of Toronto for one dollar each (Bliss, 1982). Similarly, Harvard declined in practice to profit from faculty discoveries in public health or therapeutic agents in the 1920s; in 1934 and 1935, it transformed practice into formal university policy, stipulating that neither the university nor its faculty would seek patents in these areas except for patents which it would "(dedicate) to the public" (Harvard, 1935). Over the next four decades, about a half dozen patents were dedicated to the public by Harvard (Atkinson, 1990; Bliss, 1982; Kenney, 1986; Weiner, 1987). Nevertheless, despite some concerns about the potential negative impact of patents on academic research, it is clear that, historically, the desire by universities to obtain and exploit patents did not necessarily interfere with norms and culture of academic research, including collaboration and sharing of materials and information; universities held patents and basic research flourished (Kevles, 1993).

Changing Incentives

Although scores of universities had established the means to patent the results of university research by the postwar era, a mid-1950s survey by the American Association of Universities revealed that, among some 20 leading academic institutions, only the Massachusetts Institute of Technology actively encouraged the forging of business ventures from faculty research (Apple, 1989; Etkowitz, 1990).

Commercial Biotechnology

Principle worked against commercialization, but so did the circumstances of the postwar academic enterprise. Most university research, especially in the basic life sciences, yielded little that was patentable and even less that commanded significant market value. Moreover, the pressures that had led universities to flirt with commercialization during the depression dissolved after World War II, when, in response to demands of national defense, space exploration, national health, Federal spending for basic research increased geometrically (Kevles, 1993).

By the 1960s, Federal funds for research and development (R&D) had increased some 200-fold since 1940, but the Federal budget only 11-fold; clearly, the rate of growth for R&D could not be sustained. Federal spending (in constant dollars) for academic science soon plateaued, then fell in the early 1970s. Like their predecessors in the 1930s, academic administrators sought new sources of funds. The growing commercial prospects of molecular biology, including the patentability of its products, offered the promise of being that source. That expectation stimulated the creation of a biotechnology industry in the United States. Soon, industry aggressively pursued ties to university laboratories in order to gain access to their knowledge and expertise in molecular biology (Wright, 1986).

In return campuses could expect financial dividends. Emblematic of the shift toward commercialization of biological research was Harvard; in 1974, it departed from its longstanding policy against patents and commercialization and obtained a package of grants and endowment from Monsanto that was to total \$23 million over 12 years. In return, Monsanto received an exclusive worldwide license to patents that might arise from Monsanto-supported research (Kenney, 1986). In 1975, Harvard formally adopted a new patent policy that implicitly abandoned the commitment to dedicate medically-related patents to the public (Harvard, 1975). The 1975 policy represented a fundamental shift that was intended to generate income through partnerships with industry and by transferring research results to the private sector for development (Atkinson, 1990; Harvard University, 1975).

Federal Policies

From the mid-1960s to late-1970s, the relative strength of American innovation seemed to be declining. The number of patents issued by the United States in 1978 was roughly the same--about 66,000--as it had been in 1966; the proportion issued to foreigners had almost doubled, from 20 percent to nearly 40 percent (Bremer, 1980; Dunner, 1980; Railsback 1980; Wright, 1986). Congress, eager to foster competitiveness through technological innovation, enacted the 1980 Tax Reform Act (Public Law 97-34), which allowed corporations a tax credit for increased expenditures for academic R&D.

Congress also overhauled Federal patent policy. Prior to 1980, companies wishing to exploit government patents faced 26 different sets of agency regulations (Kastenmeier, 1980). Furthermore, although NIH had institutional patent agreements with 65 universities, which allowed them the first option to patent results of NIH-supported research (Frederickson, 1976; Wade, 1977), many agencies still retained title to patents generated by their research programs. Data indicated, however, that this practice discouraged the transfer of the patented technology to the marketplace: In 1963, the Federal government held 14,000 unexpired patents, but could license only 1,200 of them; in 1975, it owned about twice as many, but again was able to license only 1,200.

Federally owned patents were public property, and the weight of principle--as well as the Department of Justice--worked to make them available for licensing on a nonexclusive basis (Kevles, 1993). The nonexclusive approach discouraged development, since delivering products to the marketplace involved risk and required capital. Nonexclusive licensing was a disincentive to commercialization (Bremer, 1980; Lonsdale, 1979; Schmitt, 1979; Stevenson, 1979): "In general, ideas owned by all will be developed by none" (Johnson, 1979). Thus, to stimulate industrial innovation of federally funded research, Congress enacted two laws. The Patent and Trademark Amendments of 1980 (also referred to as the Bayh-Dole Act of 1980; Public Law 96-517) changed the presumption of title in inventions made with Federal funds from the government to universities, small businesses, and nonprofit institutions. The Stevenson-Wydler Technology Innovation Act of

1980 (Public Law 96-480) intended to promote cooperative research and technology transfer from federal labs. (The following chapter explores these and other technology transfer laws in greater detail.)

Academic-Industry Alliances

Even before Congress had moved to encourage technology transfer, the commercial prospects of molecular biology attracted the attention of investors, and industry and university officials. From the late 1970s onward, American universities established ties to the nascent biotechnology enterprise, creating biotechnology centers and consortia to work on potentially practical subjects (Fiske, 1982; Kenney, 1986; Wall Street Journal, 1981a, 1981b, 1982b; Wright, 1986). Between 1977 and 1982, industrial patronage of universities grew from about 3 percent to more than 6 percent of academic expenditures for research (Dickson, 1984).

Coincident with increasing industrial involvement and academic patents came rising concerns about the integrity of academic research and training. University molecular biologists--unlike chemists, for example--were unaccustomed to close industry ties, which some believed offended traditional faculty principles. Some biologists believed it was improper to profit privately from knowledge gained through publicly funded research grants. Apprehension was widespread that professorial involvements in biotechnology firms, from which investigators would receive research contracts, would lead to the exploitation of university resources and students for commercial purposes (Baltimore, 1976; Christensen, 1980; Hall, 1987; Kenney, 1986; Kevles, 1993; King, 1982; Reinhold, 1980, 1981; Time, 1981). Additionally, many worried that the university environment would move toward a proprietary and secret atmosphere that ultimately would inhibit basic biological research by stifling the free exchange of materials and information (Dembart, 1980; Etkowitz, 1983; Hall, 1987; Kenney, 1986; Lancaster, 1980; Lynch, 1980; Sanger, 1980; Wright, 1986).

Nevertheless, the incentives driving academic biologists and their universities toward commercialization grew increasingly attractive. By 1980, the academic biomedical community's

general view had shifted away from the initially negative reaction to industry ties and patents on research results (Kevles, 1993; Wade, 5/80). Measured against the perspective of the past, the attitudes of the basic biomedical research community concerning patenting and commercialization have changed dramatically. Traditional resistance to both has yielded to an embrace of both. Today, the Human Genome Project moves forward against the backdrop of increased commercialism in academic science.

RESEARCHERS' ATTITUDES TOWARDS COMMERCIALIZATION

The attitudes and practices of current academic researchers are critical to discussions of the commercialization of research. In order to assess their opinions and experiences regarding the commercialization of academic research, OTA conducted a telephone survey in 1994 of 253 U.S. academic molecular biology researchers receiving grants from the NIH (app. A). Ninety-one percent of the respondents (230 respondents) felt "that there is a trend towards the commercialization of academic research." Eight percent of researchers (19 respondents) did not feel such a trend exists, and 2 percent (4 respondents) were undecided. Additionally, in 1993, OTA convened a workshop of genome researchers from 16 countries to discuss issues relating to the commercialization of research. Though the U.S. patent system varies from foreign patent systems (ch. 3), workshop participants also viewed a trend toward commercialization in biomedical research.

OTA also asked the survey population whether they strongly agreed, agreed, disagreed, or strongly disagreed with several value statements concerning the commercialization of academic research (table 5-2). Eighty-nine percent of researchers (225 respondents) agreed or strongly agreed that, "commercialization of research encourages practical application and brings medical discoveries to the public." Eighty percent (203 respondents) agreed or strongly agreed that, "commercialization of research is neither favorable nor unfavorable, but is inevitable due to decreased availability of federal research funds." Seventy-six percent (192 respondents) agreed or strongly agreed that, "commercialization of research enables researchers and research programs to receive deserved

financial reward.” Seventy-three percent (185 respondents) agreed or strongly agreed that, “commercialization of research encourages secrecy and discourages data sharing among researchers.” Sixty-one percent (154 respondents) agreed or strongly agreed that, “commercialization of research changes the incentives of researchers and research programs from scientific knowledge to financial gain.” Seventy-five percent of researchers (200 respondents) did not feel that commercialization of research was the result of increased government pressure. In general, researchers indicated support for conflict of interest rules (box 5-A).

Respondents were asked if they felt that more forums were needed to discuss the ethical and social issues involved with commercialization of academic research (Chart 5-1) Forty-nine percent (124 respondents) felt that forums were needed, citing reasons including that these issues haven’t been discussed enough, that forums could clarify public misconception, and that universities, industry, and government need to discuss their roles in benefiting society. Forty-eight percent (122 respondents) felt that forums were not needed, citing reasons including that enough forums already exist and that forums are not helpful. Three percent (7 respondents) were not sure whether forums were needed.

Patents

The 253 molecular biology researchers were questioned about their opinions towards several hypothetical patents involving DNA (table 5-3; box 5-B). There was consensus on the researchers’ personal approval and disapproval of the granting of certain types of patents. Ninety percent (228 respondents) disapproved of the patenting of a “stretch of undefined DNA”. Seventy-seven percent (194 respondents) approved of patents on a “method or process involving DNA.” Researchers’ opinions were more divided on other types of patents. Fifty-four percent (136 respondents) disapproved of patents on a “whole DNA sequence with known biological function,” while 36 percent (91 respondents) approved of such patents. Forty-nine percent (124 respondents) disapproved of patents on a “complete gene product,” while 37 percent (94 respondents) approved.” 42 percent (105 respondents) disapproved of patents on a “sequence with function as a marker, probe, or forensic

identifier,” while 47 percent (120 respondents) approved.” Participants of OTA’s international research workshop expressed the sentiment that patents on sequences of DNA without known function should not be granted, though patents on sequences with known function were more acceptable (Buys, 1993; Caskey, 1993; Cassiman, 1993; Cohen-Solal, 1993; Cook-Deegan, 1993; Givol, 1993; Poulos, 1993). Some scientists look unfavorably on patents on sequences of DNA without known function because they believe it is not fair to the scientist who later discovers the function (Buys, 1993; Caskey, 1993; Cox, 1993; D’Urso, 1993; Milstein, 1993; Pena, 1993)

The goals and impacts of patent law have been the topic of debate in the research community (Eisenberg, 1990). Surveyed researchers were asked to state if they “equated patents with secrecy or with public disclosure” (Chart 5-2). Interestingly, 25 percent (47 respondents) equated patents with secrecy and 30 percent (56 respondents) equated patents with public disclosure, while 18 percent (34 respondents) equated patents with both secrecy and public disclosure. 21 percent (38 respondents) equated patents with neither secrecy nor public disclosure, and 6 percent (9 respondents) did not give an opinion. Some workshop participants felt that patents encouraged secrecy and prevented or delayed public disclosure, while other participants felt that patents discouraged secrecy and allowed for public disclosure (Gibson, 1993; Pena, 1993).

Technology Transfer

Ninety-one percent of researchers surveyed (230 respondents) approved or strongly approved of academic research collaboration with industry in the life sciences. Additionally, researchers were aware and supportive of technology transfer processes. Eighty-seven percent of researchers (219 respondents) stated that their university had technology transfer policies. Sixty-two percent (156 respondents) of researchers surveyed stated that they “are required to disclose possibly patentable inventions to (their) university,” and 28 percent (71 respondents) stated that they were not required to do so. Sixty-three percent (159 respondents) of the researchers surveyed stated that they or members of their research team had conferred with officials at their institution about technology transfer issues

arising from their research. Of those who had conferred with officials, 38 percent conferred with them once a year, 20 percent conferred with them once every six months, 18 percent conferred with them once every three months, 16 percent conferred with them once a month, 2 percent conferred with them once a week, and 1 researcher conferred with officials more than once a week. Thirty-six percent (91 respondents) had not conferred with officials about technology transfer. Additionally, seventy percent of researchers who stated that their university had technology transfer policies (153 respondents) said that these policies had not “frustrated (them) with more paperwork burdens that (they) would rather not deal with.” Participants in the international research workshop noted that the U.S. is one of few countries to have a developed network of university technology transfer offices. Many scientists in international laboratories, particularly in developing countries, must apply for patents and perform technology transfer practices themselves (Allende, 1993; Berrera-Saldana, 1993; Matsubara, 1993; Panyim, 1993; Pena, 1993)

The surveyed researchers were asked about how strongly they expected technology transfer in the life sciences to affect some of the frequently-cited goals of technology transfer (table 5-4). Seventy-nine percent (199 respondents) expect technology transfer to have “a lot of effect on promoting public health and helping cure disease.” Sixty-five percent (165 respondents) expect technology transfer to have “a lot of effect on “promoting U.S. economic competitiveness abroad.” Fifty-one percent (130 respondents) expect technology transfer to have “a lot of effect on creating innovative spin-off companies.” Forty-five percent (114 respondents) expect technology transfer to have a lot of effect on “advancing the frontiers of science.” Researchers felt that technology transfer would have some effect on “making new discoveries public without losing rights to commercialize it,” “creating opportunities for ‘hands-on’ student learning,” and “augmenting funds for (their) research.” Additionally, 64 percent of researchers (161 respondents) expect technology transfer to have no effect on augmenting the researcher’s salary.

IMPACTS OF COMMERCIALIZATION ON RESEARCH PRACTICES

The majority of researchers reported that commercialization of research has had no effect on aspects of academic research, including publication (73 percent-- 184 respondents), research goals and priorities (70 percent-- 178 respondents), international research collaboration (68 percent--172 respondents), conflicts of interest (68 percent--172 respondents), data sharing (59 percent--148 respondents), transfer of research materials or protocols (58 percent--147 respondents), and collaboration with U.S. industry (57 percent--145 respondents) (table 5-5). Several researchers noted a positive effect of commercialization on their collaboration with U.S. industry (38 percent--95 respondents), international research collaboration (20 percent--51 respondents), and research goals and priorities (15 percent--37 respondents). Other researchers cited a negative effect of commercialization on data sharing (32 percent--80 respondents), transfer of research materials or protocols (29 percent--74 respondents), conflicts of interest (19 percent--48 respondents), and publication (19 percent--48 respondents).

Of the group of the researchers who stated that they were aware that their university had technology transfer policies, 62 percent (135 respondents) indicated that the university's technology transfer policies "had no effect on (their) research." Specifically, 97 percent of the researchers who stated that their university had technology transfer policies, (213 respondents) stated that the university's technology transfer policies had "not dissuaded [them] from pursuing basic research." Sixty-five percent (143 respondents) stated that the university's technology transfer policies had "not enabled (them) to participate in more commercially applicable research." Regarding research funding, 77 percent (168 respondents) stated that the university's technology transfer policies had "not improved the financial return on (their) research." Seventy-four percent (161 respondents) stated that the university's technology transfer policies had "not enabled (them) to receive more research funding."

Data Sharing and Transfer of Materials

Many survey respondents indicated that commercialization has affected data-sharing and transfer of material. When asked about access to another researcher's data, 44 percent (110 respondents) of researchers surveyed stated that they had been denied access to information or material they had requested from another researcher because of concerns about patents or other intellectual property rights. The results of this denial of access was a "delay in (their) research" for 84 percent of this group (92 respondents), a "significant change in research design methodology, or scope" for 47 percent (52 respondents), and "added costs" for 43 percent (47 respondents). Fifty-five percent (138 respondents) said that they had never been denied access to information or material they had requested from another researcher because of concerns about patents or other intellectual property rights. When asked about sharing their own data, however, 78 percent (196 respondents) replied that they had "not denied or delayed access to information or materials requested by another researcher because of concerns about patents or other intellectual property rights," and only 22 percent (56 respondents) admitted that patents had affected sharing their data.

Ninety-four percent (238 respondents) of researchers surveyed indicated that they had "never paid royalties to another non-commercial researcher to obtain access to information or materials" for use in their research. Fifty-eight percent (147 respondents) of the survey population or their institutions had been "asked to sign agreements providing for future revenue or sharing of intellectual property rights in discoveries resulting from the research" in order to obtain access to patented information or materials for use in their research, while 36 percent (92 respondents) had not.

Twenty-five percent of researchers surveyed (63 respondents) stated that they had "sold a research tool developed in their laboratory to a commercial lab." Only 6 percent of this group (4 respondents) said that their reason for selling the research tool was "to deter the use of (their) research tools in other laboratories." Fifty-four percent (34 respondents) sold the tool "to cover (their) expenses for the underlying research and development of the research tool." Thirty percent (19 respondents) sold the tool "to gain money to help with the cost of filing a patent on the research tool."

Seventy-three percent (185 respondents) had “never sold a research tool developed in their laboratory to a commercial lab.” Fifty-five percent of this group (101 respondents) had “no commercial laboratories (inquire) about using the tool.” Forty-six percent (85 respondents) hadn’t “developed a research tool(s) that a commercial lab would find useful.” 41 percent (75 respondents) had “shared the research tool free of charge to a company.”

Publication and Public Disclosure of Research Results

Many survey respondents indicated that commercialization has not affected research by delaying public disclosure and publication. Seventeen percent (42 respondents) had delayed publication or limited disclosure; the average of number of delays was 5 times. Eighty-three percent (210 respondents) stated that they “had not delayed publication or limited public disclosure of research results in order to preserve U.S. patent rights.” Twenty-four percent of researchers who had delayed (10 respondents) had delayed beyond the time of filing the patent applications, and none of those delays were less than a week in length. Fifty percent of those who delayed (21 respondents) had an average delay of more than one to six months, 21 percent (9 respondents) had an average delay of six months to one year, 17 percent (7 respondents) had an average delay of one week to one month, and 10 percent (4 respondents) had an average delay of more than one year. The researchers who had delayed were asked their reason for delaying publication or disclosure. Eighty-six percent (36 respondents) of those who delayed stated that “[they] chose to delay publication in order to file U.S. patents,” 38 percent (16 respondents) stated that “[their] university encouraged the delay,” and 24 percent (10 respondents) stated that “the private company supporting (their) research encouraged the delay.” The researchers who had delayed were asked about the effect of the delays on the research of their colleagues. Fifty-two percent (22 respondents) felt that the delays “had some effect, but was/were worthwhile, because it allowed me to file the patent(s),” 29 percent (12 respondents) felt that the delays had “not been long enough to have any effect on other researchers,” and 14 percent (6 respondents) felt that the delays had not had “any effect on other researchers because similar data were available from another source.” In contrast to the survey data, participants at the international

research workshop cited examples of delay of publication that negatively affected research (Gibson, 1993).

Industrial Collaboration

Many researchers were involved in collaborations with industry, and the majority of these collaborations included formal agreements about intellectual property rights. Forty-three percent (108 respondents) of the researchers surveyed stated that they were personally involved in collaborations with industry or industry-sponsored research. Seventy-three percent of those researchers (79 respondents) entered into collaborations because industry collaborations enable them to “work with researchers and equipment otherwise not available.” Sixty-three percent (68 respondents) entered into collaborations because “funding enables (them) to pursue (their) research interests.” Sixty percent (65 respondents) entered into collaborations because industry collaborations potentially enable their results to be “transformed into marketable medicines or therapies.” Of those involved in industry collaborations, 72 percent (78 respondents) have a formal agreement regarding intellectual property rights for results of their industry-sponsored research.

Research Collaboration

Almost all of the surveyed researchers were involved in academic research collaborations, most indicated that patenting and licensing agreements don't affect their collaborations, and most do not make a formal agreement regarding patents and royalties. Ninety-eight percent of the surveyed researchers (249 respondents) indicated that they were involved in non-industrial collaborations with other researchers. Ninety-one percent (229 respondents) of the surveyed researchers collaborate with other laboratories within their institutions, 90 percent (228 respondents) of researchers collaborate with researchers at other U.S. academic institutions, and 64 percent (161 respondents) of researchers collaborate with researchers at academic institutions in other countries (table 5-6).

Many sources predict that commercialization will have a large impact on academic research

collaborations, however, 84 percent of the researchers involved in collaborations (210 respondents) stated that patenting and licensing issues do not affect their collaborative research agreements at all. Twelve percent (30 respondents) stated that patenting and licensing issues affect their collaborative research agreements unfavorably, and 3 percent (8 respondents) stated that patenting and licensing issues affect their collaborative research agreements favorably.

Regarding formal research agreements, 86 percent (214 respondents) of the researchers involved in collaborations did not make a “formal written agreement on issues of patents and royalty payments for products resulting from this research.” When prompted for the reason that the researcher proceeded without a formal agreement, 51 percent (108 researchers) stated that they “did not discuss these issues with the other researchers, because (the researcher) didn’t think any commercial product would result from (their) research.” 17 percent (37 researchers) stated that “it never occurred to (the researcher) to do this,” 15 percent (32 researchers) stated that they “discussed these issues with the other researchers and agreed that (they) may need to discuss one if a commercial product results,” 7 percent (14 researchers) stated that they, “discussed these issues with the other researchers and did not expect any commercial products to result from (their) research,” 5 percent (10 researchers) stated that they, “discussed these issues with the other researchers and made an oral agreement,” and 2 percent (4 researchers) stated that they, “meant to but never got around to it.”

Thirteen percent (33 respondents) of the researchers involved in collaborations did make a “formal written agreement on issues of patents and royalty payments for products resulting from this research.” The agreement detailed information regarding intellectual property rights for 85 percent of this group (28 respondents), conditions regarding the transfer of materials for 70 percent of this group (23 respondents), regarding publication rights for 55 percent of this group (23 respondents), and regarding royalty payments for 49 percent (16 respondents) of this group (table 5-7). Participants in OTA’s international research workshop indicated that intellectual property issues had largely not affected international research agreements, however, many participants were concerned that such issues would soon play a larger role (Cook-Deegan, 1993). Participants felt that there is a need for an

international agreement on intellectual property issues relating to genetic information, and some felt the additional need for a central repository of genetic information which would own its intellectual property and donate the information to the public (Caskey, 1993; Matsubara, 1993; Mirzebekov, 1993).

PATENTING MOLECULAR BIOLOGY RESEARCH

Survey respondents reported a lack of pressure to patent molecular biology research. Ninety-six percent (244 respondents) of respondents stated that they had never “been pressured by (their) university to pursue patents on results of government-supported research when (they) would have other wise chosen not to.” Ninety-eight percent (248 respondents) of respondents stated that they had never “been pressured by (their) university to pursue patents on results of industry-supported research when (they) would have other wise chosen not to.” The 5 percent of researchers (11 respondents) who had been pressured to pursue patents on results of industry- or government-supported research were asked how this pressure had affected their research. All of these researchers (11 respondents) agreed that, “the pressure to patent has (not) forced (them) to redirect (their) research priorities to more commercially applicable areas.” Eighty-two percent of these researchers (9 respondents) said that this pressure to patent had not “given (them) additional incentive to complete (their) research. Fifty-five percent of these researchers (6 respondents) said that this pressure had “prevented (them) from freely exchanging material with other laboratories.” Ninety-one percent of these researchers (10 respondents) said that this pressure to patent had not “enabled (them) to receive deserved financial reward, that (they) might otherwise have missed.” Sixty-four percent of these researchers (7 respondents) said that this pressure had “produced frustrating paperwork and delays in (their) research.”

Patent Applications

Researchers were questioned about their activities in and motivation for filing patent applications. Forty-two percent (105 respondents) of academic molecular biologists surveyed said

that they, their university, or industrial partner had filed patent applications based on results of their research (Chart 5-3). Fifty-seven percent (144 respondents) said that patents had never been filed on their research, and 1 percent (4 respondents) of respondents weren't sure. For the group of 105 researchers whose research results were the basis of filed patents, the average number of patents filed that named them as an inventor was 22. Sixty-nine percent of the researchers had patents (72 respondents) that involved DNA, 55 percent (58 respondents) involved a laboratory procedure, 51 percent (53 respondents) involved protein, and 24 percent (25 respondents) involved RNA (Chart 5-4). Fifty-five percent (58 respondents) involved a combination of these materials and processes. Twenty-nine percent (30 respondents) involved other materials including vectors, chemical compounds, enzymes, and anti-bodies. Cross-tabulations were performed which showed that researchers who filed patents on inventions involving DNA, RNA, and protein were more likely than other researchers to approve of patents on DNA sequences of known biological function, with function as a probe, or with no known function.

Forty-eight percent of the researchers who filed patent applications (50 respondents) did so because “(the researcher) wanted a financial reward for (their) research.” Thirty-six percent of these researchers (38 respondents) filed patent applications because their “agreement to receive research funds from industry included this stipulation.” Thirty-four percent of these researchers (36 respondents) filed patent applications because their “employment agreement with the university included this stipulation.” Sixteen percent of these researchers (17 respondents) filed patent applications because their “start-up company needed the patents.” Fifteen percent of these researchers (16 respondents) filed patent applications because their “agreement with a government funding agency included this stipulation.”

Issued Patents

Forty percent (42 respondents) of the researchers who filed patents had received patents resulting from research exclusively supported by the government (table 5-8). Of this group, the

average number of patents received resulting from exclusively government-supported research was 26. Thirty-one percent (13 respondents) of this group indicated that they had personally received royalty income from licenses of patent based on their exclusively government supported research. Forty-five percent of respondents' institutions (19 respondents) had received royalty income from licenses based on respondent's research, while the academic departments of 26 percent (11 respondents) of respondents, and the laboratories of 24 percent (11 respondents) of respondents had received royalties.

Twelve percent (13 respondents) of the researchers who filed patents had received patents resulting from research exclusively supported by industry. Of this group, the average number of patents received resulting from exclusively industry-supported research was 3. Fifteen percent (2 respondents) of this group indicated that they had personally received royalty income from licenses of patent based on their exclusively industry supported research. Royalty income from licenses based on respondent's research was received by the institutions of 15 percent (2 respondents) of respondents, the academic departments of 15 percent (2 respondents) of respondents, and the laboratories of 15 percent (2 respondents) of respondents.

Twenty percent (21 respondents) of the researchers who filed patents had received patents resulting from research exclusively supported by both industry and government. Of this group, the average number of patents received resulting from exclusively industry-supported research was 2. Five percent (1 researcher) of this group indicated that they had personally received royalty income from licenses of patents based on their exclusively industry supported research. Royalty income from licenses based on respondent's research was received by institutions of 24 percent (5 respondents) of respondents, the academic departments of 14 percent (3 respondents) of respondents, and the laboratories of 14 percent (3 respondents) of respondents.

PRIVATIZATION AND COMMERCIALIZATION OF THE HUMAN GENOME PROJECT

Revolutionary advances in the life sciences since World War II led to the formation of a sector of companies, both older more established firms and newer firms, using various biotechnologies to create products for sale in markets for health care, pharmaceuticals, agriculture, waste remediation, and even mining (Berg, 1993; OTA, 1991). Moreover, Federal funding for this research built the research base necessary for biotechnology to emerge (OTA, 1984; OTA, 1988; OTA, 1991), aided in part by a relatively shorter interval between the laboratory and the marketplace compared to other scientific disciplines (Berg, 1993). Today, commercial biotechnology is a billion dollar industry, employing thousands of people.

Analysts estimate that 1,100 biotechnology companies, employing 80,000 people in the United States, generated sales of over \$4 billion in 1991 (Business Week, 1992). Another estimates sales from biotechnology products at \$7 billion in 1993 and provided 97,000 jobs (Spalding, 1993). Experts estimate gross sales of \$20 billion by the year 2000 (Longstreet, 1992). Amgen, a Southern California biotechnology company, sold over \$1 billion worth of its breakthrough drug erythropoietin (EPO) in 1992 (Spalding, 1993), indicating the scale of the market for just one protein product. The market for treating Alzheimer's disease, a genetically based disorder afflicting between 3 and 4 million people, is estimated by some experts to approach \$8 billion per year in the United States alone (Korman, 1994).

As the Human Genome Project moves forward, one of its fundamental assumptions is that it will increase understanding of genetic disorders and advance therapies for the 4,000 or so currently recognized human genetic disorders. Since its inception in 1988, the Human Genome Project has been largely a publicly funded effort--both in the United States and abroad. Nevertheless, the commercial potential of the project was recognized at the outset. With intellectual property rights at the core of commercialization potential for most of these therapies, the biotechnology sector represents a key stakeholder in the controversy surrounding the NIH patent applications for expressed sequence tags (ESTs).

Until recently, the tools used in, and most results from, research conducted as part of the Human Genome Project have not been the focus of investment interest. In addition to therapeutic and diagnostic advances, the idea was that a growing biotechnology industry could use the research undertaken by the Human Genome Project to provide the Nation with more high wage, highly skilled jobs. In effect, the project was sold to the public, in part, as an economic stimulus package (Cook-Deegan, 1993). The stage was set for human genome research to begin as a public project and then integrate with private enterprise and proprietary interest as the opportunity arose--with broad benefits to all over the course of this evolution.

Emerging Private Interest in the Human Genome Project

Capital markets in the United States, and in most other developed nations, have rushed to invest in biotechnology companies since 1980. On Oct. 14, 1980, investment bankers brought public on the New York Stock Exchange what is generally considered the first dedicated biotechnology company, Genentech; the value of its shares more than doubled in early trading. Since then, initial public offerings of biotechnology firms often energized capital markets. Venture capital funding chased scientists with recognized research results in the hope of significant returns from bringing biotechnology companies public on U.S. stock markets (Middleton, 1993). Nevertheless, over the last two years, capital markets have responded negatively to various downturns and setbacks since the initial rush of private investment in the 1980s. Since January 1992, the value of most biotechnology stocks fell with the prolonged economic downturn. In the first two quarters of 1993, the value of publicly traded biotechnology shares declined 40 percent (Stone, 1993).

Even in the face of uncertain markets, biotechnology is still a major sector receiving financing from investors on exchanges all over the world. Despite the caution of investors in the United States, biotechnology companies raised over \$5 billion in 1992. Venture capital transactions involving biotechnology companies also increased from a total value of \$217 million in 1991 to \$459 million in 1992 (DeYoung, 1993). In particular, expectations of returns from research derived from the Human

Genome Project also stand in contrast to the overall downturn. Genome related ventures in the private sector appear poised to improve the prospects for investing in biotechnology in the future. Two newly established companies, Human Genome Sciences (HGS) and Incyte, raised a total of over \$40 million in separate initial public offerings in late 1993 (Fisher, 1993).

Enthusiasm for investing in innovative biotechnology companies was slow to carry over to the Human Genome Project when it was first launched. Even in 1992, investors were ambivalent about prospects for widespread, wholesale commercialization of human genome research (Anderson, 1992). Unresolved patent issues, limited markets for diagnostics, and the slow progress of some genome research, initially made the Human Genome Project less attractive to investors, despite the acknowledged long term potential of the project (Anderson, 1992). For example, although several disease causing genes have been discovered, it is still too early to see any major product sales.

Nevertheless, as just mentioned, human genome-related research and DNA sequencing in the private sector is increasingly attracting private financing. Several new U.S. firms and nonprofit research institutes have been organized to pursue rapid sequencing of all or parts of the human genome, with the goal of selling or licensing genetic information to companies interested in developing unique therapeutic and diagnostic products (table 5-8). The Institute for Genomic Research (TIGR) is moving forward with plans to sequence as much of the expressed component of the human genome as possible, using the EST technique (Carey, 1993). Venture capital backers of TIGR established HGS as a for profit company to commercialize TIGR's research results. HGS has filed for patents on ESTs already obtained at TIGR and HGS (Cook-Deegan, 1994; Schreck, 1994b), which appears to have played a role in attracting funding from large corporate sources for TIGR of \$85 million over a ten year period (Wade, 1994). Several other genome derived companies have been organized, and established biotechnology firms, Amgen and Genentech for example, have either begun their own DNA sequencing operations or are investing in start-ups that do so (Carey, 1993).

As privatization of the Human Genome Project moves forward, at least three important questions arise. First, what impact will the privatization of human DNA sequencing have on human

genome research? Second, will patents on ESTs or other human DNA sequences serve as a catalyst for the commercialization of the human genome, or will they be an obstacle? And finally, how does the biotechnology sector (with many disparate, individual corporate research agendas across many companies) perceive intellectual property protection for human DNA sequences--with one voice or many?

Implications for Collaboration and Competition

The emerging private interest in the fruits of research on the human genome presents companies with the opportunity to compete or collaborate, sometimes simultaneously. This phenomenon can take the form of a cooperative agreement, often conducted under a strategic alliance, between two or more firms. A strategic alliance can include more vertical arrangements, such as exclusive licensing of patented research results. Some types of strategic alliances complement each other. Cooperative research usually results in some form of intellectual property that implies patent obligations and licensing rights, spelled out in an agreement of some kind. Any agreement will have some transaction cost.

Patents, or rights to commercialize patents, can be transferred from laboratory to laboratory, or from laboratory to the marketplace. The transfer depends on the terms negotiated between the parties, such as in a licensing agreement, and the price that the licensor exacts from the party receiving the rights to the patents. If the price is set too high then the transaction might not take place, and the benefits of sequencing that portion of the human genome covered by the patent could be temporarily or permanently forgone. Several experts have called for some balance of property rights with requirements for efficiency, particularly in regard to efforts by Federal laboratories to patent human DNA sequences (Eisenberg, 1993). However, the issue also applies to industry. Several industry representatives claim that transaction costs can inhibit the efficient commercialization of human DNA sequence information, especially if they are primarily useful as research tools (Hanna, 1994; Shapiro, 1994).

Strategic Alliances

One of the ways the biotechnology sector has grown is through a process of strategic alliances. These alliances can take the form of, for example, joint ventures, licensing agreements, equity investments, and mergers or acquisitions. Young biotechnology firms hungry for capital to invest in R&D have often solicited alliances with larger firms, domestic or foreign. In the human health care field these are often established pharmaceutical companies. An example of a strategic alliance could take the form of the arrangement between Lederle and Immunex, with American Cyanamid (the parent of Lederle) restructuring its oncology business with a more powerful research focus with the help of Immunex (Burrill, 1993). Numerous other examples exist that serve to illustrate the variety and the extent of strategic alliances in the biotechnology sector (Thayer, 1993). In many cases, difficult economic circumstances encourage strategic alliances.

Recent negative developments in capital markets on which biotechnology companies have traditionally relied for financing have created significant pressures to build alliances with more established firms. Prices of publicly traded shares in most dedicated biotechnology firms have dropped. By July 1993, the combined market value of 100 leading biotechnology firms had, dropped 30 percent from 1992 highs (Thayer, 1993).

For those smaller companies with relatively underdeveloped research portfolios, current capital market conditions have forced them to forgo further rounds of venture capital financing and instead, offer their shares in initial public offerings. These companies are in essence being venture financed by selling their equity through shares offered on public stock markets (Thayer, 1993), adding pressure on the companies to seek out more established firms for strategic alliances to further develop their advanced discoveries. Financing from established partners in a strategic alliance also helps to balance the uncertainty of further investment from public capital markets. In some cases, even well established biotechnology companies have sold a majority equity stake to a large foreign pharmaceutical company in order to gain access to capital, in addition to sales and distribution ability. For example, Rhone Poulenc-Rorer acquired over 60 percent of Applied Immune Sciences in 1993, and Hoffman La

Roche acquired a majority stake in Genentech in 1990, with Roche Holdings (the Swiss parent of Hoffman La Roche) owning 62 percent of Genentech (Burrill, 1994). Large pharmaceutical companies from around the world are attracted to the innovative nature of U.S. biotechnology, and become a source of capital and foreign marketing channels that U.S. biotechnology companies may turn to increasingly in the future.

Although the trend has been for larger companies to acquire or ally with smaller firms, in the past two years there has been an increase in the number of alliances between smaller U.S. biotechnology firms. Alliances between smaller U.S. biotechnology companies made up 62 percent of all alliances between U.S. firms in the biotechnology sector. Increasingly, access to foreign markets is the goal for many strategic alliances with larger overseas partners, according to data compiled by the Institute for Biotechnology Information (Thayer, 1993). For older more established corporations, both domestic and foreign an alliance with a small biotechnology company with innovative research capabilities can add new technology and products to the established firm's portfolio.

In human genome research, strategic alliances have just begun to form around sequencing and mapping ventures. HGS of Rockville, Maryland--as noted above, a commercial partner of TIGR--has given worldwide exclusive rights to SmithKline-Beecham for most diagnostic, therapeutic, and vaccine products and services based on TIGR and HGS discoveries (Gershon, 1993). SmithKline agreed to pay HGS \$125 million for these exclusive rights contingent on meeting certain milestones (Carey, 1993; Shreck, 1994b). Hoffman-La Roche Inc. agreed to enter a research collaboration agreement with Millenium Pharmaceuticals Inc. valued at \$70 million (Fisher, 1994). Other companies have also entered into the commercial sequencing effort. Incyte Pharmaceuticals of Palo Alto, California, has filed for patents on an undisclosed number of ESTs (Wuethrich, 1993). Rhone Poulenc-Rorer executives have stated they are interested in building an alliance with a partner to sequence human DNA in the hope of uncovering novel treatments for genetic diseases. Glaxo, a major British pharmaceutical company, has also advertised its desire to sequence genes with a small partner (Carey, 1993). Alliances not only depend on abundant sources of capital, but also on

researchers with the expertise to develop full scale DNA sequencing efforts and analyze the results to uncover important genes. Some posit that scientists with experience in setting up genome sequencing ventures are at risk of being “locked up” by ventures with the goal of sequencing human genes (Carey, 1993; Berg, 1993).

The “Gold Rush” Effect

Many scientists claim that the NIH filings for EST patents, although abandoned, set off a race to sequence as many cDNAs as rapidly as possible, which they fear will be inefficient and introduce obstacles to datasharing necessary for the Project’s success (Wuethrich, 1993). The rush to sequence as many genes as possible transcends national boundaries and the line between public and private efforts. Sequencing operations, private and public, in a number of countries such as Japan, are also pursuing patents on human DNA sequences (Wuethrich, 1993). According to some experts, the search for genes in general has become a “gold rush” (Carey, 1993). For example, the several gene hunting firms appear to be competing with each other for skilled personnel to execute their sequencing strategies (Carey, 1993; Cook-Deegan, 1994), in addition to staking out as much of the genome as possible. Personnel recruiters are rapidly trying to fill orders for scientists with experience in this field (Carey, 1993). Nevertheless, it is unlikely that there will be any problems justifying concern over the availability of skilled scientists. Of more concern to many is the race to identify and patent human DNA sequences, and that those patents will exclude others from exploiting the commercial potential of the human genome.

Some express concerns that patents will issue on all human genes within the “next several years,” potentially locking up the genome by a few universities, and corporations (Wuethrich, 1993). Fears of this type must be balanced by the likelihood that most of the sequencing operations stand to profit the most by ensuring that the greatest number of users have access to their sequences at a reasonable price. For example, it can be speculated that such a scenario depends on setting a price that would not be so high as to inhibit those parties who would come forward to pay for the use of,

for example, HGS or Incyte human DNA sequences. Most private sequencing operations are not interested in becoming fully integrated biopharmaceutical corporations, with their own manufacturing operations. They are interested in licensing their sequences to companies that already have the facilities capable of developing products for commercial sale (Dickinson, 1994). If companies set the price too high, it would inhibit growth in the market they seek to foster.

Most of the companies that have established operations to commercialize sequence data from the human genome focus on patenting certain portions of the genome before other institutions (Cook-Deegan, 1994), potentially leading to a rush to patent human DNA sequences. For the most part, the business strategies of these companies depend on the competitive advantage gained by identifying and patenting human DNA sequences first. It is difficult to objectively determine what positive or negative effects this could have on the overall commercial research enterprise. Nevertheless, the mere possibility of patent protection for such sequences has undoubtedly been a key attraction for those corporations and individuals investing in these companies. Most of the companies also claim that significant patent protection is not necessary for their eventual commercial success (Cook-Deegan, 1994). It remains to be seen if this is true, or if patenting would preclude the trade secrecy that many observers claim would result in the absence of patents on human DNA sequences.

IMPLICATIONS FOR COMMERCIAL BIOTECHNOLOGY

Since the early 1980s, the biotechnology and pharmaceutical industries have relied on the use of human genetic material to provide targets for drug discovery, as resources in the development of diagnostic agents and vaccines, and as essential research tools. Diagnostic and therapeutic uses of genetic material have been claimed for both partial and complete gene sequences. Genetic diagnosis based on knowledge of the DNA sequence itself--whether fragmented or whole--is the basis of much work in biotechnology companies today. In gene therapy, potential oligonucleotide-based therapies, and even protein-based therapies, the DNA sequence itself defines the drug (Vovis, 1994b). The DNA sequence and its proteins are an critical key to the development of new diagnostics. In some

cases, use can be found with partial gene sequences, in other cases, the complete gene sequence is needed.

As mentioned, the biotechnology industry was founded, in part, on the premise of patentability of genes, gene fragments, and gene products. Patents are critical for companies to ensure access to capital and attract investment. Citing a \$200 million barrier to market entry in developing drugs, industry officials rely on the patent system for obtaining a lead in getting drugs to market (Hanna, 1994; Scott, 1994). Pharmaceutical companies have long relied on the patent system for protecting proprietary interest in chemical and biological compounds. More recently, pharmaceutical and biotechnology companies have exploited this system by filing patents on large amounts of genetic information in anticipation of future applications of that information to human health (Hanna, 1994). HGS and Incyte are among the leading companies specializing in filing patents on ESTs, specifically. Nevertheless, many of the companies claim that the failure to acquire patent protection for their EST applications will not preclude commercial success (Scott, 1994; Haseltine, 1994; Cook-Deegan, 1994). Indeed, one company claims that it will use trade secrets to maintain a proprietary position in this field (Cook-Deegan, 1994; Scott, 1994).

Still with respect to EST patents, most companies believe it inappropriate to file and receive a broad reaching application for a single patent that encompasses thousands of ESTs. One concern is the potentially anti-competitive effect of one or a few individuals or companies staking wholesale claims on large amounts of the human genome. However, other industry representatives defend the practice of filing claims for large numbers of ESTs so as to preserve the national interest and enhance future commercial development. These voices argue that if U.S. companies do not file these claims, other foreign companies will--thereby damaging the U.S. competitive position (Haseltine, 1994). Moreover, because full gene sequences will be available shortly, the issue of partial versus complete will soon become moot (Scott, 1994; Haseltine, 1994).

At a January 1994 OTA workshop on "Commercial Biotechnology and Patenting Human DNA Sequences," company representatives discussed points of agreement and disagreement in the

commercial biotechnology sector regarding intellectual property protection and the Human Genome Project. Not surprisingly, the workshop participants agreed that human DNA sequences should be patentable if the criteria of novelty, nonobviousness, and utility are met. Five issues relevant to companies' interests in patents on human DNA sequences were identified:

- whether claims in patents on partial sequences preclude or dominate subsequent claims on full sequences;
- the importance of the utility criterion, particularly in establishing patent dominance;
- access to research tools associated with genome research;
- Federal patent and finding practices and policies related to the Human Genome Project; and
- the effects of Federal technology transfer policies on research collaborations.

Patents and Prior Art

As described in chapter 3, much of the debate over whether to patent partial or full gene sequences revolves around what patent attorneys would consider "prior art." What concerns industry officials are two possibilities: First, whether publishing in the literature (or making available through databases) partial gene sequences unprotected by a patent will eliminate incentives to use the gene for most purposes. And second, whether a patent on a partial sequence will preclude or dominate future use patents based on the full gene sequence.

Most workshop participants agreed that if a partial DNA sequence meets the criteria of novelty, nonobviousness, and utility, then it should not be distinguished from full-length gene sequences. Not surprisingly, they disagreed on the extent to which prior claims on partial sequences, whether published or patented, would preclude subsequent patent claims on full gene sequences. Further, there was no consensus on whether abandonment of the NIH application would provide a broadstroke resolution of these issues because PTO had initially denied NIH's claims, as many felt that any application--including those pending and any yet to be filed--must be weighed individually.

Indeed, some in industry believe that the abandonment of the NIH filings perpetuates the uncertainty regarding these issues (Waldholz, 1994), although many also believe the NIH applications did not represent the strongest test case (Hanna, 1994; OTA, 1994).

Industry also expressed concern about PTO's position on DNA sequence patents, which they perceive as internally inconsistent and in apparent contradiction with recent court rulings. It was the perception of OTA workshop participants that if, for example, a partial amino acid sequence for a protein is published in the literature, PTO will rule that a DNA sequence patent can no longer be issued for that protein because any molecular biologist can easily extrapolate back to a partial DNA sequence and from there identify the full gene sequence to the full-length gene sequence. Yet, PTO ruled, at least in the NIH application, that a partial sequence is not sufficient to receive a patent claiming the complete gene sequence (which many companies will complete by filing continuations and continuations-in-part) and gene product--a position derived from recent court rulings that a company has no claim on a partial sequence until it has found the full gene sequence (See Chapter 3).

Such perceived contradictions breed uncertainty within industry. Companies also worry that because the pace of science far exceeds the pace of testing patent validity in the courts, decisions as to what is enabling prior to 1978, for example, are quite different than they would be in 1994. It is of concern that any interpretation of a past legal ruling applied to current patent applications could be misleading.

One industry representative projected that over 1 million ESTs likely will be sequenced worldwide by the mid-1990s (Scott, 1994). If there are only 100,000 genes and the Patent Office rules that a composition of matter patent issued on an EST rules out a patent for the full gene sequence and gene product, then the necessity and desire to file patents for biotechnology inventions might decline, with a potential decline in commercial development of potentially important products. Industry officials agreed that utility of the patented matter was the paramount consideration, though no consensus could then be reached when asked to draw a bright line on what constituted utility. For example, what constitutes an acceptable definition of utility probably differs between therapeutics and

diagnostics, with requirements of the former being more stringent--i.e., patents on partial DNA sequences can be of great use for developing first-stage diagnostics (Sommercorn, 1994; Galas, 1994).

Still, despite disagreement about some details, OTA found a wide range of commercial interests believe the current system generally works well. Although companies would prefer guidance or policies from PTO--e.g., if a partial gene sequence is insufficient to obtain a patent, then knowledge (prior art) of that DNA sequence will not invalidate a future patent once the full gene has been identified--they largely have adapted to the current U.S. system.

Patent Dominance

Biotechnology officials believe the U.S. patent system does not need to be changed to accommodate the issues raised by patents on human DNA sequences, in general, and EST patents, in particular. However, the NIH application points to another generic concern though perhaps one more acute if EST patents with broad claims issue. Several commercial representatives believe that allowing one company to control an entire pathway because it patents the first step could have a chilling effect on the incentive for others to elucidate what might be the biologically important endpoint (Hanna, 1994; Shapiro, 1994). How much control should be afforded parties who invest at the front end of the discovery over those who develop and identify its applications?

As noted in chapter 3, the issue of patent dominance has a long legal history, and on face value, it appears the situation is no different for genome-related patents. Presumably cross-licensing can proceed as a matter of course (Schreck, 1994a), since such a practice generally benefits both parties. Industry is accustomed to negotiating rights and reasonable returns based on the value of an investment and negotiating potential DNA patent rights pose no new issues (Schreck, 1994a). In fact, some experts view having separate patents out of the same DNA sequence as an intended and efficient use of information because the various parties will necessarily pursue different approaches to solving a variety of problems (OTA, 1994).

Access to Research Tools

Biotechnology officials believe that the controversy surrounding the NIH patent applications and patents derived from the Human Genome Project reinforces an underlying theme common to biological and biomedical research: Unfettered access to products used as research tools is critical. Unfettered need not be free, but making patented research tools available on a nonexclusive basis to competitors and other research organizations is an essential form of information exchange that serves everyone in the long term (Shapiro, 1994). Furthermore, most argue this is especially true for research tools patented by the Federal Government or by academic research institutions that discovered the tool through Federal support. In fact, exclusive licensing of research tools by the Federal Government could lead to inappropriate competition by the government with industry (Shapiro, 1994; Haseltine, 1994). Nonexclusive licensing allows a Federal laboratory to comply with Federal technology transfer laws, while simultaneously protecting its investment and the future investment of parties who seek to employ those research tools (Shapiro, 1994; Haseltine, 1994).

U.S. Human Genome Project

When NIH tiled its applications in 1991, then director Bernadine Healy argued it was obliged to do so to comply with Federal technology transfer laws (See Chapter 6). In general, biotechnology companies support Federal technology transfer as important to the public interest, although disagreements exist on whether the types of claims in the EST application were appropriate and in the public interest. In general, biotechnology officials argue that NIH should focus on transferring technology--exclusively or through limited licensing--when discrete, specific applications might reasonably be commercialized (Haseltine, 1994).

Yet, while companies acknowledge that technology transfer was important to spawning the biotechnology industry and that Federal funding of the Human Genome Project has remarkably advanced the field and led to further commercial ventures, there was some disagreement about the future role of the Federal Government in the Human Genome Project as it becomes increasingly

privatized. Some believe that market forces will drive companies' selection of the most promising and applied areas of research for development, leaving the more basic end of the spectrum to Federal funding and investigation; others express concern that the Federal Government continues to be a player in the race to find genes, therapeutics, and diagnostics and hence competes directly with the private sector (Shapiro, 1994; Haseltine, 1994).

Most believe the shift now occurring between public and private investment in genome research and development as inevitable and intended (Scott, 1994; Shapiro, 1994; Sommercorn, 1994). The Government traditionally has made the long-term, high risk investment and developed the science to the point that the private sector can invest in it toward development.

Research Collaborations

Finally, the NIH patent applications raised issues related to research collaborations, including collaborative efforts between industry and either Federal laboratories or academic or private research institutions. With respect to research collaborations and genome-related research, industry collaboration is in its nascent stage (since the project is in its early stage), but looms as increasingly important as genome research advances. And, although not unique to genome research, OTA found a universal complaint among biotechnology firms participating at its 1994 workshop--the reasonable pricing clause of the Cooperative Research and Development Agreements (CRADAs) (OTA, 1993; ch. 6). The issue of drug pricing and CRADAs (as well as regulation of breakthrough drugs) has been analyzed by OTA elsewhere; this section briefly describes companies' general concerns.

Industry unease focuses on whether collaborations are worth the effort, given the possibility that the U.S. government either will claim ownership later or control the price of the ultimate product (Hanna, 1994). Some claim government funding affects not only industry-government interaction, but also industry-industry interaction, and ability to raise capital with companies refusing to enter into agreements with other companies whose research is partially funded by NIH, for example, because no clear stream of intellectual property rights exist (Haseltine, 1994). Others believe Federal researchers

also suffer because they are cut off from collaborations with industry, which over time might place them at a disadvantage in their field of research. In fact, one company decided to reimburse a nonprofit affiliate over \$1 million for a forgone research grant from DOE, in order to avoid uncertainty stemming from the technology transfer function in Federal laboratories (Cook-Deegan, 1994). Most companies that participated in OTA's 1994 workshop declared they currently do not, or in the future will opt not to, pursue CRADAs. In contrast, although university technology transfer offices vary in their sophistication and expectations regarding income streams resulting from collaborations, they are viewed by companies as significantly easier to negotiate with than Federal laboratories (Hanna, 1994).

Chapter 6 discusses Federal technology transfer in greater detail, but with respect to genome research, OTA found companies were generally frustrated with the CRADA process at both NIH and DOE--in particular, the multiple levels of review and the amount of time it takes to complete an agreement (OTA, 1994). Relatively speaking, however, biotechnology industry officials feel that the national laboratories are far more difficult to deal with in terms of negotiating CRADAs, although improvements in the DOE process have occurred in the past few years (Galas, 1994). Still, several genome companies appear to rely heavily on Federal technology transfer laws that confer intellectual property ownership to contractors and grantees of NIH and DOE (Cook-Deegan, 1994). Thus, ongoing Federal-industry-academic collaborations will be key to fulfilling the therapeutic and diagnostic promises of the Human Genome Project.

SUMMARY AND CONCLUSIONS

NIH's 1991 filing of patents on expressed sequence tags ignited a controversy among genome researchers around the world. Historically many researchers opposed commercialization of academic research (particularly in the biomedical sector), yet universities have sought patents on faculty research since the turn of the century. As Federal funds decreased and recombinant DNA technologies came of age in the early 1970s, academic administrators actively sought new sources of funding for research. At the same time, Congress enacted several laws that aimed to speed innovation and American competitiveness by facilitating the transfer of technology from academia to the private sector. Today, industry and academia are close partners in biomedical research.

A 1994 OTA survey of molecular biologists who receive Federal funds from NIH and discussions at a 1993 workshop of international genome scientists illuminated several attitudes of academic researchers toward patents, technology transfer, and commercialization of biomedical research. Researchers overwhelmingly agreed that a trend toward the commercialization of academic research exists. As a whole, the academic research community opposes patents on stretches of DNA without known biological function because of concerns over secrecy, cooperation, and fairness; these researchers seem more divided in their views of patents on known genes and other biological materials. Interestingly, academic a significant majority of researchers are aware of their university's technology transfer systems and generally expect the systems to be successful in meeting the goals of increasing both public health and U.S. competitiveness.

According to OTA's survey, commercialization has affected some aspects of research and has not greatly affected others. Nearly half of researchers surveyed had been denied access to another researcher's data, which delayed their research, because of concerns over intellectual property. Fifty-eight percent of respondents have been forced to sign intellectual property agreements in order to obtain access to patented information or materials. Forty-three percent of OTA's survey respondents were involved in collaborations with industry, often to work with specific researchers or equipment. However, 97 percent of surveyed researchers said that their universities technology transfer policies

had not dissuaded them from pursuing basic research. Ninety-eight percent of the survey respondents were involved in nonindustrial research collaborations and most indicated that patent issues did not affect these arrangements, and they did not make a formal agreement concerning patent rights. Most respondents had not delayed publication of research results to preserve patent rights. Though most had never felt pressured by their universities to pursue patents on their research, about half of the survey population had filed for patents based on their research, and several had been granted patents on both government and industry-supported research.

Since World War II, several biotechnology companies have created a billion dollar industry, employing thousands of people in the United States. Biotechnology receives major investments worldwide, and in the United States raised over \$5 million in 1992. Recently some firms have adopted as part of their corporate strategies an approach centered on rapid sequencing of the human genome through expressed sequence tags. As genome research becomes privatized, opportunities for collaboration and their implications for rewards are multiplying. Strategic alliances and concerns for intellectual property have created a “gold rush” effect, in which companies race to sequence and commercialize genome information. Company representatives participating in OTA’s workshop on commercial biotechnology felt that human DNA sequences should be patentable. Moreover, a wide range of commercial interests believe the current system generally works well. Most workshop participants see the current shift from public to private investment in genome research as inevitable and intended by the Federal government.

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Box 5-A--Conflict of Interest Rules: Attitudes and Effects

Recent debates have centered on proposed Federal and university conflict of interest rules which seek to maintain the objectivity of scientific research by forcing academic researchers to disclose related financial interests (Witt, 1994). OTA surveyed researchers about their opinions of conflict of interest rules. Ninety percent of researchers (227 respondents) indicated that their university had “rules governing conflict of interest.” Four percent (10 respondents) indicated that their university did not have “rules governing conflict of interest,” and 6 percent (16 respondents) were not sure. Eighty percent of researchers surveyed (202 respondents) stated that conflict of interest rules, “are necessary to ensure that all financial interests and collaborations are know, thereby enabling proper agreements to be made” (table 5-10). Seventy-one percent (179 respondents) of researchers surveyed stated that conflict of interest rules, “are necessary to protect the public interest by ensuring that researchers’ incentive is the pursuit of scientific knowledge, rather than financial gain.” Seventy-six percent (193 respondents) of researchers surveyed disagreed with the statement “Conflict of interest rules, are an invasion of researchers’ privacy.” Fifty-eight percent (147 respondents) of researchers surveyed stated that conflict of interest rules “do not burden (them) with excess paperwork,” while 35 percent (88 respondents) indicated that conflict of interest rules “do burden (them) with excess paperwork.” Fifty-five percent of researchers (140 respondents) indicated that they were “aware of proposed Federal conflict of interest rules,” 44 percent (111 respondents) were not aware of these, and 1 percent (2 respondents) were not sure.

Table 5-10--Researchers' Opinions of Conflict of Interest Rules

Do you feel that conflict of interest rules...	Yes	No	Not sure^a
are necessary to ensure that all financial interests and collaborations are known, thereby enabling proper agreements to be made?	80 Percent	13	7
are necessary to protect the public interest by ensuring that researchers' incentive is the pursuit of scientific knowledge, rather than financial gain?	71	22	0
are an invasion of researchers' privacy?	13	76	11
burden you with excess paperwork?	35	58	7

^aPercentages may not add to 100 due to rounding.

Of the 227 researchers aware of a university conflict of interest policy, 85 percent (193 respondents) stated that these rules had no effect on their research, 11 percent (24 respondents) stated that these rules had a positive effect on their research, and 4 percent (10 respondents) stated that these rules had a negative effect on their research.

SOURCE: Office of Technology Assessment, 1994.

Box 5-B--Patenting Expressed Sequence Tags

OTA surveyed academic researchers about their opinions towards NIH's 1991 filing for patents on expressed sequence tags. Sixty-three percent of the molecular biology researchers surveyed (159 respondents) were familiar with the filing. Seventy-four percent of the researchers who were familiar with the patent filing (118 respondents) disapproved of NIH's patent filing. There appeared to be some consensus on researchers' reasons for disapproval (Table 5-1 1). Eighty percent of the disapproving researchers (97 respondents) disapproved of NIH's action because "EST patents would inhibit data sharing among researchers." Seventy-nine percent (96 respondents) additionally disapproved because "patenting a gene with such minimal effect will discourage the greater efforts needed to characterize biological function and subsequent diagnostic and therapeutic use." Forty-one percent (49 respondents) disapproved because "it is not ethical for any group to patent human DNA." Thirty-six percent (44 respondents) disapproved because NIH's filing "would inhibit private investment in genome research." Twenty-eight percent (33 respondents) disapproved because, "it is not appropriate for the government to seek financial return on taxpayer supported research."

Table 5-11--Researchers' Reasons for Disapproval of NIH EST Patent Applications

"Do you disapprove of NIH's filing for EST patents because you believe..."	Percent Yes
EST patents would inhibit data sharing among researchers."	80
patenting a gene with such minimal effect will discourage the greater efforts needed to characterize biological function and subsequent diagnostic and therapeutic use."	79
it is not ethical for any group to patent human DNA."	41
it would inhibit private investment in genome research."	36
it is not appropriate for the government to seek financial return on taxpayer supported research."	28

Thirteen percent of researchers familiar with NIH's patent filing (21 respondents) approved of NIH's action, and 13 percent (20 respondents) were not sure how they felt. Seventy-six percent of the

approving researchers (16 respondents) approved because “EST patents promote the exchange of sequence information, after the information enters the public domain.” Sixty-seven percent (14 respondents) approved because “such patents will promote scanning the genome quickly and improve final mapping.” Fifty-two percent (11 respondents) approved because “EST patents would encourage private investment in genome research.” Fifty-two percent (11 respondents) approved because “NIH should seek financial return on its research.”

Sixty-two percent of researchers familiar with NIH’s patent filing (99 respondents) stated that their research would not be affected at all if the U.S. Patent and Trademark Office (PTO) granted patents for ESTs. Twenty-nine percent of researchers familiar with NIH’s patent filing (46 respondents) stated that their research would be negatively affected, and 67 percent of this group (31 respondents) felt that their research would be negatively affected because “collaboration with colleagues would be discouraged.” Interestingly, researchers predicted a more negative affect of EST patents on the research of their colleagues: 52 percent (82 respondents) felt that their colleagues research would be negatively affected. Again, the majority of those who predicted a negative affect (71 percent/ 58 respondents) felt this way because “collaboration with colleagues would be discouraged.” Additionally, 62 percent of this group (51 respondents) felt this way because PTO’s granting of EST patents “would add more pressure on their colleagues to patent or pursue more commercially applicable research.”

SOURCE: Office of Technology Assessment, 1994.

Table 5-1--International Research Funding for Human Genome Research

	Agency	Funding Amount (U.S. Dollar Equivalents)	Year
European Community	European Genome ^a Programme/ European Molecular Biology Laboratory	\$13.5 Million	1993
France	GREG ^b / CEPH ^c / INSERM/ Genethon	\$17 Million \$8 Million	1993
Germany	Deutsche Forschungs Gemeinschaft	\$5 Million	1993
Italy	Italian Genome Programme ^d	\$1.5 Million	1993
Japan	Ministry of Education (Monbusho) ^e / Science and Technology Agency ^e / Ministry of Agriculture & Fisheries, Ministry of Health, Ministry of Trade and Industry	\$20 Billion Yen \$26.51 Billion Yen \$5 Million	FY 1993 FY 1993 1993
	National Institutes of Health ^f / Department of Energy-HERL ^g	\$8.4 Billion/ \$107.8 Million	FY 1992 FY 1992
	Medical Research Council (Human Genome Mapping Project)/ Wellcome Trust (Sanger Center) ^h	\$9 Million \$15 Million	1993 1993

^a Sir W. Bodmer, "Genome Research in Europe," *Science* 256:480-481, 1992.

^b "French Genome Project Officially Launched," JPRS-EST-93-018, June 3, 1993.

^c D. Butler, "French Move Past Genethon to Gene-Therapy Research," *Nature* 361:671, 1993.

^d "Italy: Human Genome Project Advances," JPRS-EST-93-004-L, February 1, 1993.

^e "Japanese Government Agencies Increase Biotech Budgets for Fiscal 1993," *Genetic Engineering News*, P. 20, March 1, 1993.

^f NIH Data Book, 1992

^g Burdette, N.J., Office of Health and Environmental Research, U.S. Department of Energy, Genmantown, MD, personal communication, July 1993.

^h P. Aldhous, "Europe's Genomes Come Home to Roost," *Science* 260:1741, 1993.

Table 5-2--Researchers' Opinions of the Commercialization of Academic Research

	Strongly agree or agree	Strongly disagree or disagree	Not sure^a
Commercialization of research encourages practical application and brings medical discoveries to the public.	89 Percent	10	1
Commercialization of research is neither favorable nor unfavorable, but is inevitable do to decreased availability of federal research funds.	80	18	2
Commercialization of research enables researchers and research programs to receive deserved financial reward.	76	18	6
Commercialization of research encourages secrecy and discourages data sharing among researchers.	73	25	2
Commercialization of research changes the incentives of researchers and research programs from scientific knowledge to financial gain.	61	36	4
Commercialization of research is a result of increased government pressure.	20	75	5

^aPercentages may not add to 100 due to rounding.

SOURCE: Office of Technology Assessment, 1994.

Table 5-3--Researchers' Approval of Granting DNA Patents

	Disapprove	Approve	Not sure^a
Stretch of undefined DNA	90 Percent	4	6
Method or process involving DNA	18	77	6
Whole DNA sequence with known biological function (e.g. cystic fibrosis)	54	36	10
Complete gene product	49	37	14
Sequence with function as a marker, probe, or forensic identifier	42	47	11

^aPercentages may not add to 100 due to rounding.

SOURCE: Office of Technology Assessment, 1994.

Table 5-4--Researchers' Expectations of the Effectiveness of Technology Transfer in the Life Sciences

	A lot of effect	Some effect	A little effect	No effect	Not sure^a
Promoting public health and helping cure disease	79 Percent	17	2	0	2
Promoting U.S. economic competitiveness abroad	65	25	6	0	4
Creating innovative spin-off companies	51	37	6	12	4
Advancing the frontiers of science	45	40	13	1	.8
Making new discoveries public without losing rights to commercialize it	21	32	20	10	17
Creating opportunities for "hands-on" student learning	17	35	33	12	4
Augmenting funds for your research	15	39	34	9	4
Augmenting your salary	2	8	26	64	1

^aPercentages may not add to 100 due to rounding.

SOURCE: Office of Technology Assessment, 1994.

Table 5-5--Researchers' Assessment of Commercialization's Effect on Academic Research

	Positive Effect	No Effect	Negative Effect	Not sure^a
Your collaboration with industry within the U.S.	38 Percent	57	4	2
International research collaboration	20	68	8	4
Goals and priorities	15	70	14	1
Transfer of research materials or protocols	12	58	29	1
Data sharing	8	59	32	2
Conflicts of interest	8	68	19	5
Publication	8	73	19	1

^aPercentages may not add to 100 due to rounding.

SOURCE: Office of Technology Assessment, 1994.

Table 5-6--Research Collaborations

Are you involved in any collaborations with researchers in other laboratories with you institution?	Yes	No^a
at other U.S. academic institutions?	91 Percent	9
at academic institutions in another country?	90	10

^aPercentages may not add to 100 due to rounding.

SOURCE: Office of Technology Assessment, 1994.

Table 5-7--Frequency of Terms Included in Collaborative Research Agreements

	Included	Not Included	Not sure^a
Intellectual property rights	85 Percent	9	6
Conditions on the transfer of materials	70	24	6
Publication rights	55	45	0
Royalty payments	49	42	9

^aPercentages may not add to 100 due to rounding.

SOURCE: Office of Technology Assessment, 1994.

Table 5-8--Summary of Issued Patents

	Government-Sponsored Research	Industry-Sponsored Research	Government and Industry Sponsored Research
Number of Researchers who Received Patents	42	13	21
Average Number of Patents Received	26	3	2
Number of Researchers who Personally Received Royalty Income	13	2	1
Number of Researchers whose Institutions Received Royalty Income	19	2	5
Number of Researchers whose Departments Received Royalty Income	11	2	3
Number of Researchers whose Laboratories Received Royalty Income	11	2	3

SOURCE: Office of Technology Assessment, 1994.

Table 5-9--U.S. Companies Involved in Sequencing and Mapping the Human Genome

Company	Research Plan	Capitalization as of 12/93
Collaborative Research	Use of semi-automated mapping, positional cloning, and semi-automated multiplex sequencing to locate genes for therapeutic development	\$3.5 million (NASDAQ)
Darwin Molecular	Focus on rapid DNA sequencing to screen and amplify potential pharmaceuticals	Estimates of \$50 million (VC)
Human Genome Sciences	Selling or licensing genetic information from the Institute for Genomic Research to pharmaceutical companies (NASDAQ)	\$259 million
Incyte Pharmaceuticals	High speed sequencing to find genes and corresponding proteins	\$56 million (American Stock Exchange)
Mercator Genetics	Use of positional cloning or "reverse genetics" to develop common disease therapeutics	unknown (VC)
Millenium Pharmaceuticals	Use of genome mismatch scanning to isolate genes related to diseases and target them for drug development	Estimates of \$8.5 million (VC)
Myriad Genetics	Focus on development of diagnostic tests for disease genes	Estimates of \$12.3 million (VC; Eli Lilly)
Sequana Therapeutics	Use of positional cloning to find and isolate genes for diagnostic and therapeutic purposes.	Estimates of \$5 million (VC)

VC = venture capital funding

SOURCE: Office of Technology Assessment, 1994, based on R.M. Cook-Deegan, "Survey of Genome Science Corporations," contractor document prepared for the Office of Technology Assessment, U.S. Congress, January 1994; and L. Fisher, "The Investment Allure of Biotechnology Stocks," New York Times, Dec. 3, 1993.

Chart 5-1--Researchers' Opinions towards Ethical Forums

Question: Do you feel that more forums are needed to discuss the ethical and social issues involved with commercialization of academic research?

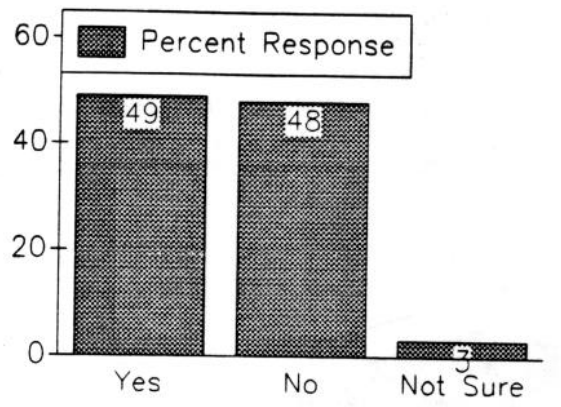


Chart 5-2--Researchers' Views of the Goals of Patents

Question: Do you equate patents with secrecy or with public disclosure?

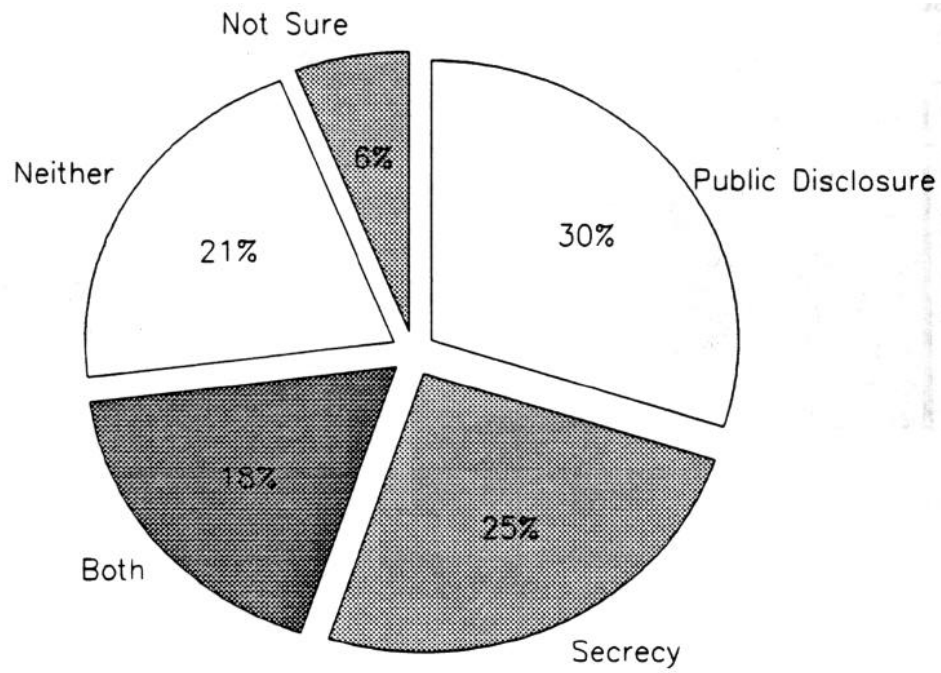


Chart 5-3--Patents and Molecular Biology Research

Question: Have patents ever been filed based on results of your research?

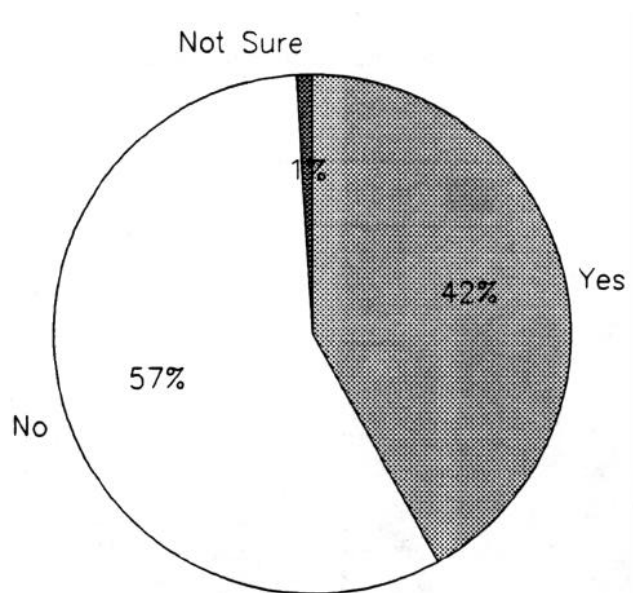
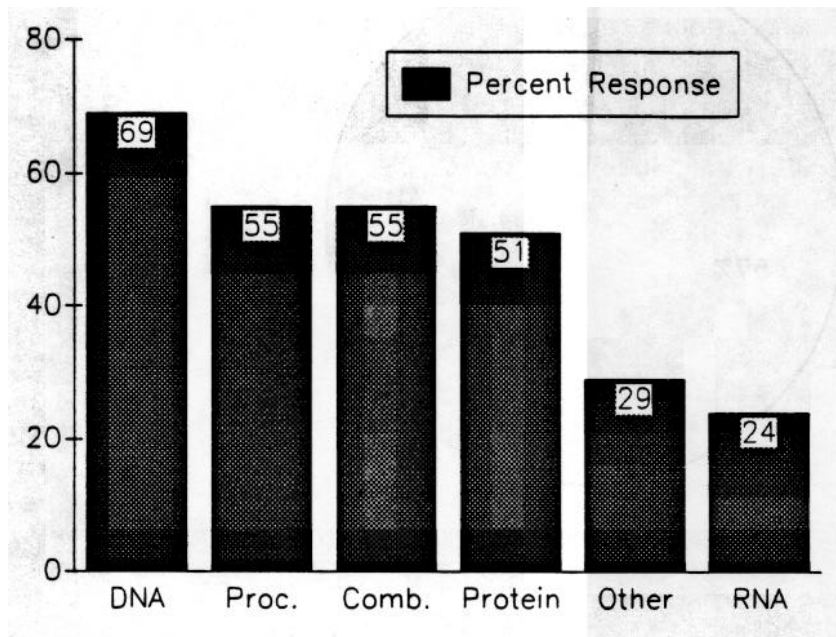


Chart 5-4--Types of Patent Applications

Question: What materials or processes did the patent involve?



CHAPTER 6

FEDERAL TECHNOLOGY TRANSFER

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Commercialization of federally funded research depends on transferring technology to industry, which translates intellectual property into commercial products. For their part, most companies are reluctant to invest the millions of dollars and time required to fine tune and develop inventions from federally funded research unless guaranteed some measure of exclusivity (Fusfeld, 1986). Human genome research is no different.

Today, an elaborate structure of laws, regulations, and policies exist to facilitate the transfer of technology to industry, including results from federally funded biomedical research efforts to the biopharmaceutical industry. Increasingly, Congress has looked to agencies supporting science and technology, including the National Institutes of Health (NIH) and the Department of Energy, to promote economic competitiveness. Indeed, it was in this climate that NIH officials and researchers decided to pursue patents for expressed sequence tags (Healy, 1992; Adler, 1992).

HISTORICAL PERSPECTIVE

In the 15 years following the end of World War II, the Federal Government became the major source of funding for research and development (R&D) in the United States. Today, the Federal Government funds nearly half of R&D performed in the United States, largely to meet public objectives such as national defense, space exploration, improved health, greater food production, and energy conservation. For the last 30 years, however, the Federal Government has undertaken the additional responsibility of supporting the Nation's scientific and technical enterprise for the purpose of economic competitiveness.

The notion that the Federal Government should play a direct and active role in stimulating R&D as it relates to economic growth first came under scrutiny during the Kennedy Administration through the President's Science Advisory Committee's recommendations regarding industrial innovation (Averch, 1985). Later, President Nixon's Council of Economic Advisors encouraged more active partnerships between the public and private sectors in research and technological innovation, and President Carter's Domestic Policy Review explored what steps the Federal Government should take to encourage industrial innovation (Logsdon, 1986). These broad appeals for an activist role of government in stimulating R&D eventually evolved into what is currently known as "technology transfer."

Technology transfer is the process by which results of R&D are applied and used in another area, organization, or commercial sector. The term has different meanings in different contexts. It can refer to the legal and administrative process by which the transfer of legal rights--such as the assignment of a patent to a contractor or the licensing of a government owned patent to a company--is achieved. Or, it can refer to the informal movement of information, knowledge, and skill from a Federal laboratory to the private sector through person to person contact or collaboration. The most crucial economic aspect of technology transfer, however, is the use of a research derived product or a process in a new commercial enterprise.

The concept of domestic technology transfer as an activity of the Federal government is not new and arises from an interest in promoting economic growth (Rahm, 1988). The Federal Government has always had laws and policies encouraging innovation, dating back to the Patent Act

of 1790 (Roessner, 1988). The U.S. Department of Agriculture (USDA) has been transferring technology for over a century, beginning with the establishment of the land grant colleges under the Morrill Act in 1882. The Hatch Act of 1887 created agricultural research stations separate from the university system. The goals of these laws were to improve agricultural productivity through direct education of farmers by providing them with the latest research results and intervening in farming practices to increase yield. Thus, there were both commercial and public interest motivations behind the legislation (Hornig, 1984).

Federal domestic technology transfer has been appreciated by some officials in both the executive and legislative branches, but never with as much enthusiasm as in the 1980s, when concern grew about the ability of U.S. business to compete in international markets. The sentiment that pervaded discussions in Congress, the executive branch, and industry was that American “know how,” often generated from public investment, was being transferred with increasing frequency to foreign nations only to return to the United States as commercial products (Rahm, 1988). Furthermore, few of the inventions reported to the U.S. Patent and Trademark Office (PTO) by the Federal Government each year were ever licensed for commercial use (NRC, 1987). At the same time, American industry was becoming increasingly aware that other nations were challenging its long held position of technological supremacy, and that its competitive edge in many sectors was in jeopardy (Gray, 1986; President’s Commission, 1985). The growing consensus that competitiveness was linked to innovation, and that research and technology transfer played a critical role in the Nation’s ability to compete, led industry to express greater interest in creating and strengthening its own connections with the scientific community (Gray, 1986).

Congress looked to science conducted in academic laboratories as the first and foremost place for technology transfer to begin. There tended to be more openness in university laboratories than government laboratories, because many Federal laboratories were created to develop nuclear weapons and were therefore restricted to the public. Additionally, significant barriers had been placed to prevent technology transfer from government laboratories because of national security concerns. Nearly every statement on America's economic situation of the 1970s cites the university as the source of new scientific and technological breakthroughs, and university-industry partnerships as the vehicle through which sustained economic recovery could be achieved (Kenney, 1986). Thus, during the 1970s, new relationships between universities and industry emerged, involving such activities as industrial support of academic research, opportunities for academic consulting, research collaborations, research consortia, shared equipment use, and publications and conferences (Reimers, 1984). In the 1980s, attention also began to focus on drawing resources of commercial potential out of Federal laboratories.

This chapter focuses on the recent legislative and policy history of U.S. technology transfer. It also examines the organizational mechanisms for technology transfer at NIH and the U.S. Department of Energy (DOE), and how biomedical research results, particularly human DNA sequence patents, fits into the Federal technology transfer environment. The chapter draws on two OTA surveys that examine the current state of technology transfer from the U.S. government to industry, and from federally supported research performed at nonprofit research institutions to industry through Cooperative Research and Development Agreements (CRADAs), which are

collaborative research arrangements between Federal laboratories and nonFederal parties authorized under congressional legislation. Overall, the chapter's examination of technology transfer is confined to the United States and, except where noted, does not analyze either the transfer of technology across borders or the practices of other countries. Questions surrounding the implications of DNA patents for both academic and industry researchers are examined in chapter 5.

TECHNOLOGY TRANSFER LEGISLATION

Several laws enacted over the past 13 years encourage the transfer of technology from federally funded research. Some arise exclusively from concern about the state of technology transfer for U.S. government laboratories, while other laws address technology transfer of research funded by the Government but performed at academic institutions.

This section briefly describes the principal U.S. laws related to technology transfer. Additionally, since technology transfer frequently falls under the jurisdiction of Federal laws, regulations, and policies not explicitly designed for oversight of technology transfer processes, antitrust laws, tax laws, and other policies and initiatives that can affect technology transfer are briefly outlined.

The Bayh-Dole Act of 1980

The Bayh-Dole Act of 1980 (Public Law 96-5 17) was the first in the series of recent attempts by Congress to enhance the flow of federally funded science and technology to the private sector,

primarily in response to concerns about the health of the economy and United States' manufacturing industries. The late 1970s and early 1980s were characterized by an unprecedented period of combined high unemployment and high rates of inflation. Policymakers turned to technology transfer, in part to help rebuild what some experts believed was a deteriorating industrial sciences and technology infrastructure. This theme of economic competitiveness would continue to run through most of the politics governing technology transfer during the 1980s. Indeed, the 1990s have seen the issues of economic competitiveness and technology transfer assume a greater portion of the Federal Government's agenda.

Bayh-Dole was intended to provide a set of broad Federal rules governing patent law that could be used to enhance technology transfer from the Federal Government to industry, based on the belief that the private sector would do a better job than Federal agencies of commercializing results of U.S. government funded research (Rudolph, 1993). Previous policies had promoted the concept that if the public pays for the research, then the results should be available at no cost to the public (Homig, 1984). Private parties retained patent rights via a title in contractor policy, which meant that small businesses and nonprofit organizations, including universities, could retain title to the fruits of federally funded R&D contracts. Prior to Bayh-Dole, some Federal agencies allowed contractors to retain title to their inventions, but Bayh-Dole was the first legislation mandating a comprehensive Federal implementation of the title in contractor policy. Bayh-Dole changed the statute that constrained Federal agencies from allowing their small business and nonprofit research contractors to keep and use the results of their federally funded research.

Bayh-Dole, however, had some limitations, For example, it did not cover Government owned, contractor operated facilities. As a result, Bayh-Dole excluded a significant portion of Federal research--primarily DOE's national laboratories, which were established early in the Cold War to work on defense related technologies, and university operated, DOE owned facilities. Not until Bayh-Dole was amended in 1984 (Public Law 98-620) could Federal agencies include research contracts with universities to operate DOE's national laboratories within the scope of the title in contractor policy (Rudolph, 1992). The 1984 amendments ratified a memorandum signed by President Reagan in 1983 that directed all Federal agencies that were not specifically prevented by statute from doing so, to treat all contractors in accordance with the Bayh-Dole Act. The 1984 amendments also provided statutory authority for the Government to dispose of patent rights to contractors and made the Department of Commerce (DOC) the lead Federal agency for technology transfer matters (Rudolph, 1992).

The Stevenson-Wydler Act of 1980

In the same year that Congress passed the Bayh-Dole Act, it enacted the Stevenson-Wydler Technology Transfer Act of 1980 (Public Law 96-480, also called the Technology Innovation Act). It established an explicit precedent for the United States to try to leverage its massive investments in R&D (Rudolph, 1993). Stevenson-Wydler codified several policies to ensure that the Government had full use of its extensive investments in science and technology, particularly if the use was within the mission of the agency conducting the research. However, Stevenson-Wydler only granted

permission to fulfill these functions. It did not state that technology transfer was a statutory requirement (Rudolph, 1992).

As part of the attempt to leverage Federal investment in science and technology, Stevenson-Wydler stated that the U.S. government should endeavor to transfer technology developed at Federal facilities to State and local governments and, wherever appropriate, the private sector. Also explicitly stated in Stevenson-Wydler, is a requirement that Federal agencies administering research establish an Office of Research and Technology Applications (ORTA) at all government operated, or contractor operated laboratories with an annual budget over \$20 million. Under Stevenson-Wydler, Federal agencies may spend up to 0.5 percent of their research budgets to support of technology transfer at their ORTAs, but no more. Additionally, all of the ORTAs are coordinated by the Federal Laboratory Consortium for Technology Transfer.

Stevenson-Wydler also provides general guidance for the efforts that the Government should take to encourage technology transfer. It states that it is Government's responsibility to ensure full utilization of the results of the Federal investment in research and development (Rudolph, 1992). But for the most part, Stevenson-Wydler acknowledged the value of technology transfer as an important economic function, and legitimized grass roots efforts to transfer technology at the national laboratories but provided no means for enforcing the provision for the ORTAs (Grissom, 1992). As a result, few agencies paid attention to requirements to establish ORTAs or involve industry in cooperative projects. None of this was lost on critics of the law, who said it was ineffective because much of its funding was withheld by Congress and, as a result, agencies had neither the personnel nor

resources to comply (Gladstone, 1986; Stark, 1985). During 1985 hearings on technology transfer, the chair of the Federal Laboratory Consortium for Technology Transfer testified that of 69 technical facilities supported by Government funding, less than half had a full-time person assigned to technology transfer and three-quarters had no stated policy or procedure for encouraging technology transfer (Stark, 1985).

The Federal Technology Transfer Act of 1986

When it became apparent that relatively few technologies were being transferred from Federal laboratories after enactment of Bayh-Dole and Stevenson-Wydler, Congress amended Stevenson-Wydler with the Federal Technology Transfer Act (FTTA) of 1986 (Public Law 99-502), in large part to address uncertainties about the need for technology transfer. Legislative hearings and debate prior to passage dwelled on the looming trade imbalance, which by the mid- 1980s had extended to key high technology areas, specifically microelectronics (U.S. Congress, House, 1985). A report from the President's Commission on Industrial Competitiveness cited the creation and application of new technology as one of the four major ways in which the United States could become more competitive. A recommendation from the Commission stated the Federal Government should manage its R&D with more concern for commercial application and economic competitiveness (President's Commission, 1985). Legislative debate surrounding FTFTA focused on how best to share Federal R&D resources, including personnel, with commercial entities. FTFTA moved the discussion of technology transfer beyond the patent provisions of Bayh-Dole to more general discussions on how to facilitate cooperative R&D (U.S. Congress, House, 1985).

FTTA strengthened Stevenson-Wydler and extended the authority to explicitly promote the economic competitiveness of American industry. FTTA altered the emphasis of Stevenson-Wydler from one of permitting the transfer of technology from Federal laboratories to requiring that agencies act vigorously to transfer technology and work more closely with industry for successful technology transfer. FTTA detailed specific measures to remedy uncertainties about technology transfer at Federal laboratories operated by the Government. It did not, however, address technology transfer based on cooperative research at Federal facilities operated by contractors.

The signature feature of FTTA is the authority granted to Federal agencies to negotiate Cooperative Research and Development Agreements (CRADAs) with nonFederal parties, provided that the joint research falls within the originally chartered mission of the laboratory. The initiating and negotiating authority specifically rests with the laboratory's director, with final approval of CRADAs coming from agency headquarters in certain, limited cases. Once a CRADA was approved, the research could begin, but no Federal funds could be used to conduct the research. Laboratories were authorized to accept, retain, and utilize funds, personnel, services, property, technical facilities, and other existing resources contributed from partners to the agreement. In return, the laboratory could furnish personnel, services, property, and technical facilities to the joint research project.

FTTA also authorized award programs for Federal employees who invented or discovered anything of commercial worth, and specified that royalties from an invention that the agency retained rights to should be shared with the individual employee, up to \$100,000 annually (Rudolph, 1992).

And when the agencies themselves did not retain ownership, or promote any commercialization whatsoever, for an invention or discovery at a Federal facility, the employee responsible for the discovery is free to pursue a patent individually. FTTA also mandated that federal agencies conducting R&D allocate a small fraction of their budgets to the Federal Laboratory Consortium (FLC), an interagency group that was first set up by several defense laboratories in 1971 (Grissom, 1992). FTTA also established several policies for the laboratories to follow, including:

- technology transfer is a responsibility of each science professional and should be included in a position description as well as an annual performance evaluation;
- each laboratory having 200 or more full time scientists or engineers must devote at least one full time career professional to the facility's ORTA;
- laboratories shall participate, wherever possible, with local, State and regional authorities to promote local economic development.

FTTA directed Federal agencies to encourage, sponsor, and facilitate wherever feasible, cooperative research and technology transfer with outside parties, particularly industry, at the agencies' laboratories (Rudolph, 1992). It required the head of each agency conducting research to identify and encourage persons to act as third-party brokers to facilitate technology transfer between a laboratory and a potential user (Rudolph, 1992). FTTA also established a new technology share program, requiring the agency heads to select one or more laboratories as the focal point for using their particular areas of scientific expertise, in consortia with university and industry members. The laboratories were authorized to contribute up to \$5 million annually to each consortium (Grissom, 1992). Moreover, the Secretary of Defense was specifically ordered to take appropriate steps to

improve technology transfer from defense laboratories to the civilian sector. As part of the Order, the Department of Defense was required to make some efforts to overcome security classification barriers to technology transfer from defense laboratories to industry, but it would always be difficult to measure any changes resulting from this requirement. For example, today complaints are still common about barriers to industry because of the security classification system in Department of Defense and Department of Energy facilities (Dodd, 1993). The implementation order also required that technology access and intellectual property protection be part of the negotiations of any cooperative or sponsored research agreement with foreign corporations or governments.

The Omnibus Trade and Competitiveness Act of 1988

The central goal of the Omnibus Trade and Competitiveness Act (OTCA) of 1988 (Public Law 100-418) was to enhance U.S. economic competitiveness in relation to other nations and encouraging technology transfer from the Federal Government to industry was one of several solutions the law offered. OTCA established a technology extension program made up of several regional centers to transfer manufacturing technologies within DOC. It also changed the name of the National Bureau of Standards to the National Institute of Standards and Technology (NIST); and authorized NIST to administer the Advanced Technology Program. OTCA also authorized several studies to examine cooperative research between Federal laboratories, universities, and industry. OTCA also amended prior technology transfer legislation to provide for greater technical information dissemination of scientific research conducted overseas, as well as increased the capabilities of NTIS.

The National Competitiveness Technology Transfer Act of 1989

In 1989, Congress enacted the National Competitiveness Technology Transfer Act (NCTTA) (Public Law 101-189) in a further attempt to open up Federal laboratories to outside interests and commercialization. NCTTA authorized DOE to enter into CRADAs with industry at contractor operated national laboratories on equal footing with its government operated laboratories. With the NCTTA's enactment, all of DOE's research technically became available to industry on the same basis under standardized terms. NCTTA gives preference for CRADAs to small businesses, companies manufacturing in the United States, or foreign firms from countries that permit U.S. firms to enter into similar agreements (Grissom, 1992). In the case of Government owned, contractor operated laboratories, NCTTA required that conflict of interest provisions regarding CRADAs must be included in the laboratories' operating contracts. Interestingly, NCTTA also amended the Freedom of Information Act (Public Law 89-487) to allow Federal laboratories to withhold from public disclosure certain proprietary types of information resulting from cooperative or sponsored research with industry (Grissom, 1992).

Following the NCTTA's enactment, the interest of industry in engaging in cooperative research with Federal research laboratories began to accelerate (Grissom, 1992). Particularly affected were the large contractor operated national laboratories, such as Los Alamos, Lawrence Livermore, Oak Ridge, and Argonne. Researchers from these and other Federal facilities increasingly interacted with colleagues at scientific conferences. Many private intermediary organizations, such as venture capital firms, nonprofit professional associations, and even publishing companies, have attempted to

accelerate efforts to facilitate the commercial exploitation of the Federal investment in science and technology (Grissom, 1992; Lazarus, 1993).

Other Laws and Policies

The technology transfer process is multifaceted. In fact, regardless of whether a U.S. government agency is involved, U.S. laws and policies not explicitly designed to govern technology transfer nevertheless affect it. Today, government has enacted economic regulations, tariffs, tax laws, subsidies, and other actions that affect technology transfer, primarily in response to specific interests. These laws and policies exist without a more formal, coordinated technology policy (Roessner, 1988). Examples pertinent to this study include antitrust law, conflict of interest policies, tax laws, and funding initiatives. A comprehensive review of the nature and impact of these disparate areas is beyond the scope of this report. This section briefly highlights a few factors that affect technology transfer in order to illustrate the range of mechanisms by which the effectiveness of technology transfer efforts might be evaluated.

Antitrust Laws

Antitrust laws have affected both public and private efforts--research consortia, patent pooling, licensing agreements, joint ventures, and other alliances--to commercialize technologies in several sectors, including microelectronics, aerospace, electric vehicles, and biotechnology (Gotts, 1993; Maggs, 1991). In general, antitrust enforcement has relaxed since the 1960s and 1970s, which

theoretically increased flexibility for businesses to pursue strategic objectives. In some cases legislation has been introduced to codify exemptions for cooperative research (Maggs, 1991).

With an eye toward investing in the economic competitiveness of the U.S. technology base, several U.S. government sponsored consortia have been established with public and private funds. Most of these consortia are explicitly chartered to conduct research and sponsor development of technologies that U.S. industry can exploit to compete in global markets for high technology products. For example, in the biotechnology sector, the Biotechnology Research and Development Corporation, a joint seven company-USDA research consortium in Illinois, spends approximately \$4 million per year on biotechnology research with agricultural applications. Individual private sector consortium members have initial rights to negotiate nonexclusive and exclusive licenses from the consortium, in support of technology transfer (Maggs, 1991).

Such efforts could be problematic from an antitrust standpoint. To allow these consortia and similar alliances to form without threat of antitrust enforcement, Congress passed the National Cooperative Research Act of 1984 (Public Law 98-462). The most frequently justified exemption from antitrust enforcement under this law is that most research consortia focus on developing precompetitive technologies that are generic and open to application by all U.S. firms in a particular sector. No U.S. firms are explicitly excluded from joining the consortium if they invest a minimum amount in projects undertaken by the group. The law even allows consortia to form without the participation of a Federal agency, so long as the consortium satisfies the criteria outlined in the law

for basic research. It is interesting to note that companies in an industry will create a consortium for the sole purpose of entering into a CRADA with a Federal laboratory (Blumenthal, 1993).

Antitrust laws are intended to promote competition in the markets for goods and services. Because a patent is a legal form of a monopoly, antitrust issues sometimes emerge and affect licensing agreements or joint ventures. DOJ guidelines specify nine forms of licensing behavior that qualify for investigation by the Department (Gotts, 1993), and DOJ has initiated investigations into licensing agreements and alliances in the biotechnology sector. In one case, a cross licensing agreement between Schering-Plough and Hoffman La Roche was delayed by a Federal Trade Commission (FTC) investigation that alleged Hoffman La Roche had improperly obtained its patent on a method of mass producing a form of the drug interferon. Based on reports that Schering-Plough and Hoffman La Roche had agreed not to contest each other's patents by crosslicensing two related patents for producing interferon in a bid to comer the market, the FTC claimed that the patent claims constituted part of a larger plan to restrict entry (Gotts, 1993); the case is still pending.

It is unclear how antitrust law would affect technology transfer from a Federal agency to industry. However, where anticompetitive practices result, the possibility of antitrust enforcement could play a role.

Conflict of Interest

Conflict of interest is an area that draws increasing attention from policymakers. Conflict of interest issues with respect to technology transfer have emerged as a subject of considerable

controversy, particularly the issue of whether it inhibits technology transfer. In this context, conflict of interest refers to “a clash between public interest and the private pecuniary interest of the individual concerned” (Black, 1979). The concern over conflict of interest in the case of technology transfer is often based on the fear that a researcher or administrator, responsible for a discovery that a company is interested in licensing, might prejudice the outcome of the negotiations based on a financial relationship with the company. Many experts have claimed that policies and rules governing conflict of interest are too vague and need to be more explicit (Blumenthal, 1986). Others claim that conflict of interest concerns can inhibit the process of transferring technology out of the laboratory and into the marketplace. Even the appearance of conflict of interest can inhibit technology transfer, particularly in the biotechnology sector (Blumenthal, 1986).

Academic-Industry-Government relationships in the context of biomedical research can be controversial and complicated by conflict of interest issues. Conflict of interest restrictions also seek to prohibit or deter conflicts between official public duties of a government employee and the employee’s personal financial interests (18 U.S.C 208). These provisions seek to serve the public’s interest by prohibiting or regulating possible influences upon the public official that might arise from the personal financial holdings, dealings, or ownerships of the Government employee or his or her immediate family, or from current or prospective employment in the private sector (Maskell, 1985).

Provisions relating to conflict of interest for Federal employees are based on Federal laws and regulations (Maskell, 1985). DOJ is responsible for investigating conflict of interest cases and enforcing all Federal conflict of interest laws. As required by Office of Personnel Management

regulations, agencies promulgate their own regulations and prescribe additional standards of ethical conduct as needed because of the special activities of that agency (U.S. Office of Government Ethics, 1988). Each agency is instructed to provide ethics counseling, guidance, and advice to its employees, and to keep its employees informed of ethical requirements and current standards of conduct.

Government conflict of interest regulation also applies to nongovernment institutions. The Public Health Service (PHS) has published proposed guidelines for recipients of extramural research grants (Cheston, 1993), which, as a condition of funding, must be embodied in each grantees' conflict of interest policy. At a scientific conference in early 1993, one DOE official blamed some of the difficulty of dealing with the bureaucracy involved in administering technology transfer on the fear of conflict of interest regulations in general, along with the potential for vigorous DOJ investigation coupled with congressional oversight (Lewis, 1993).

Tax Laws and Policies

Fiscal policy, embodied in the tax laws, can play an important role in technology transfer in several ways. In 1954, the Internal Revenue Service began to affect commercial innovation when it implemented a rule that allowed businesses to treat R&D expenditures as current business expenses for tax purposes (Roessner, 1988). Regularly renewed by Congress since enactment, the Economic Recovery Tax Act of 1981 (Public Law 97-34) provides tax credits for R&D within the company or if under contract to another organization, such as a university. In a 1985 survey of biotechnology companies, 20 percent reported that they had benefited from ERTA. Survey respondents claimed

that ERTA was important in promoting their support of university research (Blumenthal, 1994). Industrial support for research frequently augments Federal funding for research at a university and inventions become eligible for technology transfer under Bayh-Dole (Cullen, 1993).

Proposed tax credits also can affect the flow of money to research, and hence, potentially to technology transfer processes. Using tax credits for R&D is part of a corporation's financial planning for future expenditures and resource allocation. All other things being equal, if R&D expenses can be deducted from Federal tax payments, R&D will likely be stimulated, either in a corporate laboratory or the university where the firm sponsors the research. Again the potential then exists to create a larger research base that offers greater opportunities for technology transfer and commercialization. However, there is no guarantee that such a tax credit will enhance opportunities for technology transfer.

Guidelines exist for Federal government licensing professionals that are primarily designed to illustrate the significant Federal income tax consequences for both parties involved in an intellectual property transaction (Paul, 1992). For example, the licensee to any technology may deduct, as a business expense, payments made to the licensor from the licensee's Federal tax returns. In addition, there may be tax advantages, depending on the specific nature of the transaction, to the licensor. If the intellectual property transaction meets certain threshold qualifications, the transfer is treated as a sale. In this case, the seller may deduct the unamortized capital costs of the technology being transferred, and also claim capital gains tax treatment (Paul, 1992). Moreover, the cost of a patent can be amortized over the patent term. The transfer of technology to foreign entities can also create

tax advantages, depending on the characteristics of the transfer. This serves to illustrate that the tax code may be used to encourage technology transfer, whether through licensing or the assignment of patent rights. However, any consideration of tax codes as an instrument of technology transfer policy must also balance the potential costs of any changes, such as bureaucratic complexity and unintended loophole effects. Nonprofit research institutions also risk jeopardizing their tax exempt status, depending on the nature of cooperative research relationships with industrial partners.

Funding Initiatives

Funding for technology transfer and commercialization occurs at the national, State and local levels. Federal funds for technology transfer are set aside according to the Stevenson-Wydler Act of 1980--to be used by ORTAs--so that the technology transfer process will not be starved for money at Federal laboratories. Similarly funding for the FLC is earmarked from each large laboratory's budget. Most funding for technology transfer based on research at Federal laboratories, is appropriated through Congress. Another funding initiative through NIST is the Advanced Technology Program (ATP).

ATP is designed to help U.S. companies bring innovative technologies to civilian applications in the marketplace. Through ATP, NIST awards funds to successful applicants, and then provides development and technology transfer assistance to help the companies get closer to commercializing their work. ATP is generally viewed as a successful government initiative (Lazarus, 1993). However, under ATP rules, rights to intellectual property emerging from ATP consortium R&D are

automatically assigned to the industrial partner, even if a university participates in the R&D process. The universities are concerned that this could erode their rights granted under Bayh-Dole to title of federally funded inventions arising from research performed at universities.

TECHNOLOGY TRANSFER AT NIH AND DOE

Patents obtained on U.S. government supported research results, through the legal and administrative processes at the researching institution or agency, are governed by the statutes outlined in the previous section. NIH and DOE have adapted these laws to their unique organizations and established functional policies reflecting the technology transfer legislation passed by Congress, and other laws, policies, and initiatives as they apply.

U.S. government research laboratories perform a significant fraction of all R&D in the United States. As the pressures to commercialize government supported research increase, the various departments and agencies have established and modified the policies and processes governing the transfer of technology to nongovernment parties. NIH and DOE are among the leading agencies facilitating public investment in scientific research, particularly biomedical research. This section will briefly review the nature of the technology transfer processes at these two Federal agencies.

Scale and Scope of Research at NIH and DOE

NIH supports the largest Federal infrastructure for biomedical research. Historically it has funded a broad range of scientists working within the institutes themselves, and in other research

environments, such as universities, through extramural funding. The majority of Federal funding for health care related research in the United States has been distributed via NIH through individual investigator grants and program project grants (Lichtenstein, 1993). Moreover, the variety of scientific disciplines involved in NIH funded research crosses the spectrum of basic and applied sciences, from biology to computer science. In fiscal year 1992, NIH spent approximately \$8.4 billion on biomedical research. By comparison, the Federal government as a whole spent \$11.6 billion for biomedical research in fiscal year 1992 (NIH Data Book, 1992).

DOE also represents a substantial Federal investment in many disciplines of science and technology, including biomedical research through DOE's Health Effects and Life Sciences Division. In response to the strategic threat from the former Soviet Union after World War II, Congress authorized DOE to establish the national laboratories to develop weapons and technologies. DOE contracted with several major U.S. corporations and research universities to manage research at national laboratories. Some of this defense based research has found application outside of the defense establishment. For example, research on the human genome initially was undertaken at DOE to analyze the genetic effects of radiation poisoning. In fiscal 1992, DOE spent \$6.5 billion on research (OTA, 1993), of which \$107.8 million was through the Health Effects and Life Sciences Division (Burdette, 1993).

The growth of molecular technologies as new tools for the application of basic biological knowledge and the enormous potential for commercial gain from such discoveries set the stage for new institutional arrangements between government, universities and industry. Federal funding in

support of research at universities has played a key role in technology transfer to the private sector by allowing exclusive licenses to be negotiated with industry, where exclusivity is particularly important (Adler, 1992; GAO, 1992).

Intellectual capital is the main resource of the biotechnology industry and much of that capital is housed in Federal and university laboratories (OTA, 1988). In 1980, Stanford University and the University of California received the Cohen-Boyer patent, which grants exclusive use of a genetic engineering method. To date the Cohen-Boyer patent is Stanford's most lucrative patent, accruing royalty revenues of \$14,660,699 in fiscal year 1992 alone (Lehrman, 1993). Intellectual property issues have dominated much of the debate regarding technology transfer in biomedical research. Policy actions began in the courts with a series of decisions culminating in the 1980 Diamond v. Chakrabarty decision of the U.S. Supreme Court, which declared artificially created, oil-eating microbes patentable. The idea that living things--even genetically altered living things developed in the laboratory--could be considered as inventions, and therefore patentable, was then a startling new concept (Clutter, 1992).

Technology Transfer at NIH

NIH officials argue that technology transfer in biotechnology historically has been accomplished through patent activities and is a particularly legitimate form of technology transfer in a climate of uncertainty (Adler, 1992; Healy, 1992). NIH policy specifically states that "NIH/ADAMHA [sic] recognize that under the FTTA and the patent licensing law to which it refers,

Congress and the President have chosen to utilize the patent system as the primary mechanism for transferring Government inventions to the private sector” (Patent Policy Board, 1992). Patent protection is viewed as especially necessary to stimulate product development in the pharmaceutical and biotechnology industries where the demonstration of efficacy and safety is lengthy and extremely expensive. Whether inventions are patentable could determine whether research efforts are accelerated (Adler, 1992). Thus, much of the technology transfer activities of NIH center on the establishment of cooperative research relationships, and any patents and licenses that might follow a successful collaboration.

NIH Technology Transfer Infrastructure

With the passage of FTTA, the ORTA and patent functions previously in NIH’s Office of Medical Applications of Research were transferred to a new Office of Invention Development, later renamed the Office of Technology Transfer (OTT). The Office of Invention Development, prior to becoming OTT, provided staff support for the NIH Patent Policy Board and frequently conducted forums to bring NIH scientists and industrial representatives together (GAO, 1989).

OTT is responsible for pursuing patent protection for intramural NIH research. In the case of the NIH DNA patent applications, OTT received the invention disclosure and processed the patent filings in accordance with OTT’s determination that such an action was its responsibility under U.S. patent and technology transfer statutes (Healy, 1992). In addition, each institute and center within NIH maintains a technology transfer office. For example, at the National Center for Human Genome

Research (NCHGR), the Technology Development Program promotes technology transfer at NCHGR.

In general, OTT's technology transfer responsibilities include developing policy and procedures, drafting of model agreements, patenting intellectual property, and licensing patented inventions (figure 6-1). The patent process begins when employee invention reports are submitted to OTT. Approximately 300 EIRs are received annually, and around 200 EIRs are processed for patent filing (Adler, 1993). The process of finding potential licensees can potentially begin as soon as the EIR is received by OTT. OTT's licensing efforts include:

- promotion of technologies at conferences and meetings;
- publication of an annual directory on technology transfer activities at NIH;
- an on-line abstract of Public Health Services technologies; and
- a database of companies and their interest by technological field for direct marketing of PHS technologies to industry.

In 1987, the NIH Director and the Administrator of the former ADAMHA established the NIH Patent Policy Board to develop overall policies for technology transfer at these agencies. Additionally, NIH agreed to manage technology and administer all aspects of the FTTA for ADAMHA and Centers for Disease Control. The NIH Patent Policy Board interacts with more senior oversight committees, such as the PHS Technology Management Board. The NIH Patent Policy Board has four Subcommittees that address specific issues:

- The CRADA Subcommittee reviews all CRADAs involving exclusive patent license rights, assesses their appropriateness, and makes recommendations regarding the CRADAs to the Patent Policy Board. As adopted by NIH/ADAMHA, a CRADA is a standardized agreement intended to provide an appropriate legal framework for, and to expedite approval of, cooperative R&D projects.
- The Royalty Distribution Subcommittee makes policy recommendations on royalty distribution, as well as on the uses of royalty income as an incentive for additional technology transfer.
- The Training Subcommittee develops materials and gives training sessions to educate the NIH/ADAMHA community on all aspects of the FTTA.
- The NIH Technology Development Coordinators Subcommittee meets monthly to discuss procedures for implementing the FTTA and to share experiences (Patent Policy Board, 1992).

In 1991, the Patent Branch was transferred out of the NIH Office of the General Counsel into OTT, where it continues to prepare and file, or contract for filing U.S. patents on NIH/ADAMHA/CDC research. Much of the patent preparation and prosecution is conducted by private law firms through contract (Patent Policy Board, 1992).

The Technology Licensing Branch of OTT handles marketing of inventions to biomedical companies. A commercial marketability analysis is made by the technology licensing branch on each patent filed. Licensing specialists have divided PHS' invention portfolio into categories that reflect market sectors such as AIDS, central nervous system, or cancer-related inventions (Patent Policy Board, 1992). Licensing is conducted on a worldwide basis, as most pharmaceutical companies are transnational and even domestic biotechnology firms require global patent protection to secure foreign markets or to form strategic alliances with foreign companies. OTT negotiates CRADA-

related licenses, but OTT and NTIS both negotiate licenses for technology developed outside the CRADA process (Patent Policy Board, 1992). According to OTT officials, NTIS lacks depth and expertise in handling licensing negotiations for NIH (Adler, 1993).

If the collaboration results in a license with subsequent royalties, the Royalty Distribution Subcommittee apportions payment. The inventor is eligible to receive 25 percent of the first \$50,000 earned, 20 percent of the second \$50,000 earned, and 15 percent of any amount in excess of \$100,000. The NIH Division of Financial Management receives NIH-generated licensing income as well as income from the all intramural licensing activities. It then distributes royalty payments to inventors, allocates funds to cover administrative overhead costs, and distributes the remaining royalties to the appropriate Institute, Center, or Bureau (Patent Policy Board, 1992).

Because FTTA emphasizes a decentralized technology transfer system, each Institute, Center, or Bureau has responsibilities for implementing and monitoring technology transfer objectives. Each must properly file invention disclosures, negotiate CRADAs, make recommendations regarding patenting and licensing, and distribute royalties within the organization. A Technology Development Coordinator in each organization has responsibility for all FTTA-related transactions. In the case of CRADAs, the Technology Development Coordinator interacts with the scientist and the collaborating company in the development, negotiation, and implementation of the CRADA, as well as subsequent patenting and licensing activities.

Prospects for NIH

NIH has made extensive use of its authority to enter into CRADAs with private firms. Nevertheless, controversy over NIH oversight of pharmaceutical pricing, particularly in the CRADA language has emerged (Washington Fax, 1993). Controversy over the fairness of a firm getting a boost over its competitors in the marketplace by entering an NIH CRADA, has also surfaced (Rudolph, 1993). In this context, some observers suggest that sometimes the technology transfer process operates well enough when government inventions are not uniformly patented, nor licensed exclusively to one private party (Eisenberg, 1993). According to corporate participants of an OTA workshop held in early in 1994, precedents exist for limited exclusive licenses to a number of qualified companies capable of commercializing human DNA sequences obtained at NIH (Hanna, 1994).

NIH appears slated for a period of generally slow research funding growth. Moreover, because most NIH royalties from commercial applications of NIH research are based on inventions and discoveries prior to 1986, OTT's most recent technology transfer efforts have not born much fruit yet (Adler, 1993). Only after the eight to ten years of researcher and clinical trials required by FDA does the product enter the market to generate revenue for NIH. Even then, problems with collecting royalty payments from licensees exist. No single individual at OTT is responsible for overseeing collection of royalty revenues (Adler, 1993).

Technology Transfer at DOE

Technology transfer at DOE and its predecessor agencies--the Atomic Energy Commission and the Energy Research and Development Administration--has a long history. Since enactment of the Atomic Energy Act of 1954 (Public Law XX-XX, Ch. 1073), DOE has included technology transfer as part of its program efforts (Decker, 1988). In response to Stevenson-Wydler, DOE established an R&D Laboratory Technology Transfer Program, managed by the Office of Energy Research, to create the institutional framework for its technology transfer.

In response to increasing pressure to find constructive civilian applications of technology developed through the extensive national laboratory structure of the DOE, the Energy Research Advisory Board offered a set of recommendations in 1988 for increasing technology transfer at DOE. The board recommended increasing DOE's technology transfer activities, developing a strong policy statement encouraging such activities, developing a high level program to ensure that U.S. firms are aware of opportunities at DOE, improving intellectual property and authorization procedures, and encouraging personnel exchange activities aimed at increasing technology transfer (U.S. DOE, 1988).

A 1983 report from the board had cited DOE's patent policy as among the most significant barriers to cooperative relationships with industry and effective technology transfer (U.S. DOE, 1983); many of those barriers, however, were removed through the technology transfer legislation passed in the 1980s. FTTA and NCCTA not only permitted contractor operated facilities to enter into CRADAs, but authorized DOE management to enter directly into CRADAs and required DOE to expedite reviews of CRADA applications.

In 1991, the Secretary of Energy reorganized DOE's management of science and technology by establishing the Office of the Science and Technology Advisor. The reorganization was a part of DOE's Enhanced Technology Transfer Program, created in response to the National Competitiveness Act. A Director of Technology Utilization is responsible for addressing DOE-wide issues related to technology transfer policies and implementation. The Director serves as a liaison with industry, academia, and State and local governments. The Director also prepares informational documents regarding technology transfer activities (U.S. DOE, 1992). Like NIH, DOE annually publishes a guide to research, patents, and licensing opportunities of national laboratories (U.S. DOE, 1992b).

The National Laboratories

The DOE laboratories and facilities perform about \$6.6 billion in R&D each year (U.S. DOE, 1992). Each DOE laboratory has a technology transfer office, which has statutory authority to use CRADAs and other collaborative agreements to transfer technology to the marketplace. A model CRADA serves as the basis for initiating individual CRADAs. Major disparities between the model CRADA and a CRADA submitted for approval to DOE officials can slow down the approval process, which is conducted through field offices and DOE headquarters in Washington, DC (Hightower, 1993). In general, a model CRADA contains a statement of work, estimated funding contributions of both parties, clarity regarding retainment of property, a product liability article, proprietary information, intellectual property and licensing requirements, and reporting requirements. In addition to administering CRADAs, DOE and DOE-supported laboratories sponsor conferences and seminars, and license technologies (U.S. DOE, 1992a).

DOE laboratories and facility contractors can often, but not always, retain title to inventions they develop (U.S. DOE, 1992a). Each laboratory or facility contractor licenses its own patents and DOE headquarters licenses government-owned patents. Each laboratory and facility operator can, within broad guidelines, negotiate terms and conditions for their technology licenses. Each advertises licensing opportunities through press releases, trade conferences, and informational mailings. Other mechanisms available for industry to work with DOE and its contractor operated laboratories include: personnel exchanges, data exchange agreements, use of specialized facilities, cost-shared procurements, cooperative agreements, patent and software licensing, reimbursable work for others, and technical assistance (U.S. DOE, 1992).

There has been a dramatic increase in the number of CRADAs administered by DOE, from 80 in January 1992 to about 300 by the end of the same year. The laboratories conducting the bulk of DOE life sciences research amenable to technology transfer include Argonne National Laboratory, Brookhaven National Laboratory, Lawrence Berkeley Laboratory, Lawrence Livermore National Laboratory, and Los Alamos National Laboratory. Biomedical related CRADAs encompass research in drug development, diagnostics, therapeutics, and basic DNA sequencing.

A recent survey of industry's views toward the national laboratories reached several conclusions. The survey population was drawn from the corporate membership of the Industrial Research Institute, a private trade association that represents 85 percent of industrial research performed in the United States. Participants were asked about their interactions with Federal laboratories. According to the companies' chief technical officers, Federal laboratories are a valuable

resource for research of a more basic nature, but few companies thought that licensing technology already developed and patented from the laboratories was worth the trouble (Roessner, 1993).

Interactions at the researcher level were viewed more favorably. The dominant reason to enter into a relationship with a Federal laboratory is to gain access to unique technical and human resources that the company could not afford to reproduce by itself (Roessner, 1993). U.S. industries benefited most, from their own perspective, when they could leverage a joint research relationship, in the form of a simple technical assistance, a CRADA, or reimbursable work-for-others agreement, with Federal laboratories (Roessner, 1993).

Prospects for DOE

OTA's 1993 report *Defense Conversion: Redirecting R&D* found that, in the short run, the national laboratories and DOE face an immediate need to streamline the process of initiating collaborative research, while adapting to increasingly severe budget constraints. In the long run, the national laboratories will need to adapt to the changing interests of Congress, the President, and DOE itself (OTA, 1993). As technology transfer efforts increase in importance, DOE and the laboratories must improve the performance of the technology transfer function at DOE. At the heart of the issue is the tension between the original statutory missions of the laboratories and the more recent pressure to work with industry to develop civilian technologies. The latent economic value of the national laboratories to the nation is hard to quantify, but many experts believe DOE has not tapped the laboratories' potential (Lazarus, 1993; Dodd, 1993).

Technology Transfer at Nonprofit Research Institutions

The United States is uniquely endowed with a rich academic biomedical research infrastructure in the form of the nation's public and private universities, and nonprofit research institutions. These institutions benefit from the level of support provided by Federal Government sponsorship, and in return they deliver the world's preeminent body of biomedical research results. Moreover, Federal research agencies' support has helped to build an academic infrastructure that benefits private enterprise, individual citizens, as well as foreign firms and foreign governments.

Compared to the long history of many American research entities, technology transfer by U.S. nonprofit research institutions is only now formally part of these institutions' establishments. Considerable controversy exists over the transfer of taxpayer supported technology to private interests. Fear of commercial corruption of research at U.S. universities has motivated many critics to decry such arrangements (Krimsky, 1991). In many ways, the evolution of concerns about industrial sponsorship of academic research that were hotly debated in the early 1980s are instructive for similar issues in government-industry collaborations. Concerns about the commercialization of academic biomedical research probably reached a watershed around 1981, about the same time Congress first held hearings on the subject (U.S. Congress, House, 1981). The hearings focused on two major issues: Do university-industry research relationships violate scientific and academic freedom and responsibilities? And do these relationships best serve the interests of the American public? Nearly one year later when a second set of hearings was held, some of the initial controversy had subsided (U.S. Congress, House, 1982). However, persistent issues relating to the management

of academic-industry relationships still challenge technology transfer at nonprofit research institutions today (Blumenthal, 1992).

Bayh-Dole significantly boosted the technology transfer function at U.S. academic institutions, and licensing of federally supported research results has increased gradually and steadily since then. According to the Association of University Technology Managers, a professional association for university technology transfer officials, revenue to U.S. universities from technology licensing agreements grows by 25 percent annually (Deener, 1993). This same growth is observed in the increasing number of technology transfer and licensing offices at U.S. universities, and in the number of invention disclosures from faculty conducting research. Indeed, almost 1,500 patents were issued in 1992 to universities and colleges in the United States alone, four times as many issued to U.S. universities in 1982 (Deener, 1993). Moreover, many universities also pursue patent protection in foreign markets as well.

Technology transfer has, over time, become an institutionalized part of most universities' goals, but not without stirring up controversy. In 1980, Harvard University proposed establishing a private corporation to transfer technology to companies in order to profit from its research. Harvard retracted the plan soon after it was aired in public, but recently was able to resurrect similar plans with little controversy (Anderson, 1992). In a more recent case in 1993, the Harvard Medical School allocated \$90 million to create a showcase for its biomedical research, and has invited venture capitalists to help develop the research for the health care marketplace (Deener, 1993). However, the University of California (UC) had to shelve its recently announced plans to establish a technology

transfer venture, called the University of California Technology Development Company. UC abandoned the plans because of the outcry from faculty members complaining that their academic integrity could be compromised if the venture took shape as planned (Science, 1993). On the other hand, technology transfer is sometimes viewed as auxiliary to, rather than competitive with, the goals of U.S. research universities--education, discovery, and the dissemination of knowledge (Nelsen, 1993). That is, the primary mission of technology transfer is to foster research and assure that research results are made available to the public in a meaningful way.

The Role of Academic Research Institutions in Extramural Research

Most Federal support for research at nonprofit research institutions, particularly universities, occurs in the form of contracts, sponsored research agreements, and extramural research awards granted on a competitive, peer reviewed, basis. Extramural research grants to individual investigators allow scientists to choose their topic of research and how it will be performed. In some cases, sponsored research and contracts involve a company or government agency approaching the researcher, or researcher's institution, with a topic to be examined and sometimes a plan for how the research shall be carried out. Nevertheless, academic institutions and individual researchers approach companies with proposals for research funding, particularly as Federal support levels off.

Examining the ratio of extramural to intramural funding clearly demonstrates the importance of academic research institutions to technology development. Extramural programs at NIH comprise

approximately 85 percent of research funds spent by NIH, and nearly all current NIH funding for the Human Genome Project has supported extramural research.

Clearly, the vast majority of genome research currently in progress is being performed at academic institutions. For fiscal year 1992, NIH spent \$8.4 billion on research, of which extramural funding totaled nearly \$6.9 billion, or roughly 82 percent of NIH's total research spending. Total funding for research on the human genome via NCHGR was \$78.6 million in fiscal year 1992 (Rufo, 1993). Extramural funding for research at academic research institutions that same year represented virtually all research funding at NCHGR in fiscal 1992. Intramural human genome research at NCHGR is just slated to begin at \$24.4 million in fiscal year 1994, depending on the final appropriations from Congress.

DOE relies heavily on its national laboratories for research that supports DOE's many missions. But, extramural research performed at universities and nonprofit institutions is still a significant portion of DOE's contribution to the Human Genome Project. In the health effects and life science field, DOE spent \$47.4 million on human genome related research in fiscal 1992 (Burdette, 1993). Of this, DOE spent approximately \$19.2 million on extramural research at universities and other research institutions (Drell, 1993). For fiscal year 1992, extramural research funding at academic research institutions represented 41 percent of DOE research on the human genome.

OTA Survey Results

In July 1993, OTA conducted a survey to examine technology transfer for federally funded research conducted at universities and nonprofit research institutions. To gather data and gain insights into the strengths and weaknesses of current technology transfer under the Bayh-Dole Act and FTTA, OTA selected a sample of the 45 largest recipients of funds from either NIH or DOE (life sciences only). The final sample is reduced from a theoretical 90 institutions because some institutions receive funding from both NIH and DOE; it also was pared down by excluding all for profit companies, foreign research organizations, and recipients performing nonscientific functions. Based on these qualifications, a total of 62 academic research institutions were surveyed and 50 responded.

Survey questions asked for both quantitative and qualitative data, under the assumption that technology transfer officials would be a key source for understanding technology transfer at academic research institutions. Many questions asked for subjective information from respondents because the firsthand experience of these officials could be as important to understanding academic technology transfer as any quantitative data.

Quantitative data include invention disclosures, patent filings, exclusive and nonexclusive licenses, and gross income from exclusive and nonexclusive licenses for the institutions' fiscal years 1991 and 1992. The survey focused on NIH and DOE life sciences research, and for comparative purposes, all U.S. government supported research at these institutions. Income from exclusive and nonexclusive licenses is the focus of analysis, since it is the sole financial indicator of the productivity of NIH and DOE research funding at academic institutions. Exclusive licensing income

is examined separately from nonexclusive licensing income in a few select instances. The data allow a rough characterization of both licensing strategies, which could prove useful to assess the merits of proposals to mandate nonexclusive licensing of U.S. government research.

The range of licensing income responses was broad, from zero to several high, outlying responses. Income over \$1 million is defined as “high,” in the sample. For example, 1992 income from exclusive licenses based on NIH supported research was \$12.9 million at the institution reporting the most income, with the next highest response dropping to about \$3.3 million. The median response for 1992 exclusive license income was \$102,500. OTA found an even greater range of responses to questions about income from nonexclusive licenses. The 1992 income from nonexclusive licenses based on NIH supported research ranged from zero to nearly \$15 million, with five institutions accounting for over 90 percent of income. The median response for 1992 income from nonexclusive licenses was \$21,200. For 1992 total income, from both exclusive and nonexclusive licenses based on NIH supported research, the median response was \$248,325. For life sciences research supported by DOE, 1992 income from exclusive licenses ranged from zero to \$837,000, with only seven institutions reporting exclusive licensing income that year. The survey found 1992 income from nonexclusive licenses based on DOE supported life science research ranged from zero--at 46 institutions--to just over \$90,000, with the other three institutions receiving income of about \$11,000 or less. In 1992, only ten institutions reported some income from licenses to DOE supported technology. Interestingly, in only one case did an institution receiving significant income from nonexclusive licenses also receive significant income from exclusive licensing agreements. In all other cases, institutions reporting higher than average income from exclusive licenses reported

relatively little or no income from nonexclusive licenses. The institutions reported a cumulative total for fiscal year 1992 of \$87.74 million of income from NIH licenses and almost \$1.65 million from DOE licenses.

A few institutions appear to have received significantly more income from exclusive licensing agreements than their peer institutions. Although the Bayh-Dole Act was passed in 1980, it has taken almost a decade for most academic institutions to begin to see royalties emerge from patents on their federally funded discoveries. Even at institutions with mature programs, the technology transfer function is barely self-supporting. It should also be noted that income from licensing usually takes months, or even years, to accrue. After years of research have ended in a discovery, and the often long patent process has successfully run its course, it takes months or even years to find a party interested in licensing the technology. All of this increases the time it takes in most cases to obtain a return on research. Based on the income data, DOE supported life sciences research appears significantly less productive for extramural academic research institutions. However, DOE research in the life sciences is more commonly conducted at large, contractor-operated Federal laboratories, instead of academic research institutions.

Based on nonexclusive licensing income data, it appears that a handful of institutions have exploited enabling or breakthrough inventions to license nonexclusively for significant income. But for those institutions that license breakthrough research results nonexclusively, returns can be significant; the data do not allow for conclusions concerning the nature of the research being licensed. However, enabling breakthrough technologies are usually appropriate for nonexclusive

licensing, as Stanford's Cohen-Boyer patent illustrates--from this patent and the many nonexclusive licenses based on it, the biotechnology sector emerged.

OTA's survey also probed respondent's views of the primary goals of the technology transfer function at each academic research institution. Technology transfer officials were asked to score eight categories according to relative importance (8=most important, 1=least important). The goals, listed in no particular order, were:

- to promote local or regional economic development;
- to augment the research budget of the institution;
- to augment the discretionary income of the institution;
- to fulfill laws obligating the transfer of federally funded technology to the public;
- to stimulate more commercially applicable research at the institution;
- to help create innovative spinoff companies based on the institution's research;
- to assist staff at the institution in establishing industrial research arrangements; and
- other (list).

Twenty-four institutions cited fulfilling Federal technology transfer laws as the most important goal of their technology transfer function. Eighteen institutions cited the "other" category as the most important, and nearly all wrote in the goal best summarized as "to benefit society through the commercialization of research." One official wrote in the blank space, "to protect faculty inventions" as the chief goal, calling attention to the patenting function in the technology transfer process.

Although subjective, OTA's survey results indicate that Federal technology transfer statutes are viewed seriously by technology transfer officials at nonprofit research institutions, probably because, consistent with the sampling method for this survey, so much research at these institutions has been funded by the U.S. government and is therefore subject to Federal law. Also of interest, the technology transfer function at most nonprofit research institutions, primarily universities, is viewed as part of the larger social mission of the institutions. Almost all responses written in the blank space provided next to the "other" category identified the goal of benefiting society through commercialization of research, which is consistent with what university officials have publicly stated concerning the purpose of academic technology transfer function (Vest, 1993). Helping to create innovative spinoff companies based on research performed at the institutions surveyed was the least important of the goals presented in the survey, according to most technology transfer officials.

A set of questions examined the effectiveness of common methods of technology transfer at these institutions. Methods of technology transfer at academic institutions include exclusive licensing, nonexclusive licensing, sponsored research agreements, technical assistance, direct investment in licensees, setting up spinoff companies, exchange of personnel, and site visits. The institutions characterized the methods as: not effective (=1), effective (=2), or very effective (=3). All but two institutions responded to these questions.

Data from the survey show that exclusive licensing is viewed as the most effective method of transferring technology at these institutions, with all but four institutions responding that it was very effective and only one of those four claiming it was not effective at all. Exclusive licensing was

followed by sponsored research agreements with twenty institutions claiming sponsored research as very effective and two designating sponsored research as ineffective. Nonexclusive licensing and setting up spinoff companies were both viewed as the next most effective means of transferring technology. Nonexclusive licensing was perceived as very effective by ten institutions, and not effective by another ten. Establishing spinoff companies to commercialize academic research was viewed as very effective by eleven institutions, with nine claiming it ineffective. According to the institutions surveyed, direct investment in licensees was believed to be an ineffective technology transfer method by 32 institutions, with two designating it as very effective. Opportunities for investing in licensees, or receiving equity in a small startup as part of a licensing arrangement, are likely to increase in the future, if major universities continue trying to set up venture capital funds or incubators to commercialize academic science. These efforts are still being pursued cautiously because of the controversy they generate at U.S. universities (Lehrman, 1993).

Another set of questions tried to elicit the most serious obstacles to technology transfer at these institutions. Three institutions did not respond to the questions, which asked the respondents to rank from 1 (most significant) to 10 (least significant) the following list of potential obstacles, in no particular order:

- cost of patenting discoveries;
- appearance of conflict of interest;
- lack of industry interest;
- lack of researcher or faculty interest;
- compliance with U.S. government technology transfer laws;

- difficulty of attracting skilled technology transfer personnel;
- conflicts between local and U.S. government requirements;
- industry reluctance to accept nonexclusive licenses;
- industry reluctance to meet royalty demands;
- unproven state of academic technology; and
- other (list).

Twenty-eight institutions said the unproven state of academic technology was the most significant barrier; another 11 institutions ranked it as the second most significant barrier. Interestingly, three institutions ranked it among the least significant barriers to effective technology transfer. Twelve institutions ranked the lack of industry interest as the most significant barrier, and 18 claimed lack of industry interest as the second most severe barrier to technology transfer. Four institutions did not view it as a significant barrier. The next most significant barrier, according to the institutions, is the cost of patenting academic discoveries. Eight institutions claimed patenting costs as their first or second most significant barrier. Federal technology transfer laws and regulations, and conflicts between local and Federal requirements regarding technology transfer, are viewed as the least significant barriers to technology transfer. All but one of the respondents felt that conflicts between Federal and local governments impede technology transfer. One institution viewed Federal technology transfer laws as the second most significant obstacle, and four others felt Federal laws are the third most severe obstacle. The rest perceived Federal laws as less of a problem. Interestingly, one institution claimed conflict of interest issues are the second most significant obstacle, and three others cited conflict of interest as the third most significant obstacle to technology transfer. Three

institutions wrote in the blank space that fewer funds available for research are the most significant obstacle to technology transfer. One other complained that the U.S. tax code creates disincentives amounting to the most serious obstacle to technology transfer. A recent gathering of university officials proposed that government establish a permanent R&D tax credit to encourage greater support by industry of university research (Washington Fax, 1994).

Data from questions about obstacles to technology transfer at these institutions indicate that Federal laws and regulations do not interfere with technology transfer in most cases. The most serious obstacles stem from the normal uncertainty about the value of new discoveries and technologies derived from basic academic research. Neither industry nor these institutions are at fault, per se. Industry can be tentative about basic research, but the respondents' interface with industry does not appear to be a serious problem. Survey data show that for all but two institutions, industry aversion to nonexclusive licensing terms is not a significant obstacle. In three institutions, industry dislike of royalty demands is viewed as an obstacle.

OTA also sought comments on the effects of Federal regulations that require reporting of invention disclosures based on federally funded research. For 26 institutions, the regulations, on balance, had no effect. For 18 institutions, the reporting requirement was burdensome to some degree. However, six institutions commented that the reporting requirements aided the technology transfer process.

OTA also probed the flexibility of certain negotiated issues or provisions of standard licensing agreements. The issues included controls on data access, restrictions on the release of data,

payment schedules, the structure of royalties and licensing fees, ownership of patent rights, issues of liability, dispute resolution, and allocation of patenting costs. The institutions identified themselves as: not flexible (=1), flexible (=2), or very flexible (=3) for each licensing provision or issue just listed.

According to OTA's data, the institutions surveyed are more flexible regarding issues such as royalties, fees, and payment schedules. Somewhat less flexible, but still subject to negotiation, are issues relating to patent cost distribution, dispute resolution, and control over access to scientific data. According to respondents, licensing provisions relating to patent ownership and liability issues are generally not subject to negotiation for companies wishing to license discoveries at academic research institutions. Moreover, seven of the institutions claim they are generally less flexible if the technology in question was discovered using Federal funds.

The survey also asked how net income from royalties and fees is distributed within the institutions. The various institutions had licensing royalty distribution policies that allocated income to the inventor(s), sometimes to the inventor's laboratory, the inventor's academic department or school, to the institution itself, and sometimes to the office responsible for technology transfer. The proportion of royalty income going to the inventor(s) ranged from 15 to 50 percent, and in 13 institutions, the inventor's laboratory would receive anywhere from 10 to 47.5 percent. The institutions received royalty income ranging from 7.5 to 75 percent. On average, the inventor received 32 percent of royalty income, and the institutions themselves received an equal share of 32 percent. One institution reported having no formula for distributing royalty income because it had no

licenses or other activities from which any income could accrue. Many institutions claimed that the income went into a research fund, or a patent fund. In any case, income of this nature is generally viewed as discretionary. There were no differences in how royalty income from federally funded and privately funded research was treated at the institutions participating in the survey.

The survey explored the timing of the patenting function as part of the technology transfer process at nonprofit research institutions. The survey asked what proportion of cases involved seeking a licensing agreement with a company before pursuing a patent on a discovery, and how often the institution is successful in doing so. On average, the institutions seek potential licensees before pursuing patent protection 53 percent of the time, and they are successful 22 percent of the time. For NIH funded research in particular, the institutions seek out potential licensees 50 percent of the time, and are successful 21 percent of the time. For DOE funded research, potential licensees are sought before pursuing a patent 29 percent of the time, and are found on average 12 percent of the time. It is easier to justify the expense of pursuing patent protection on a discovery if a company interested in licensing has already been found. However, it appears that for NIH funded discoveries at these institutions, it is generally easier to find prospective licensees than for DOE funded discoveries.

OTA also asked how respondents conduct marketing of their new technologies. A total of 47 institutions have the inventor identify potentially interested companies, on average 48 percent of the time. At 46 institutions, on average 61 percent of the time, technologies are offered to key firms that the technology transfer officials know are commercializing related technologies. At 37 institutions,

on average of 31 percent of the time, local or regional firms are canvassed **by** mail, telephone, or site visit. Thirty-three institutions turned to companies already engaged in research at their institutions, on average 16 percent of the time. At 27 of the 50 institutions, on average 25 percent of technologies are published in a database frequently examined by interested parties. And finally, 20 respondents relinquish the marketing of their technologies to an outside party, on average 10 percent of the time.

Another series of questions examined licensing of discoveries without applying for patents. Institutions were asked if they had ever licensed a discovery, other than software, without ever intending to file for a patent, and whether the research leading up to the discovery funded by NIH or DOE. In fiscal year 1992, 37 institutions had done so for a total of 80 discoveries. An average of 53 percent of those were based on research funded by NIH, and one discovery in fiscal 1992 was based on research funded by DOE. According to data from follow-up questions, most of these discoveries were biological materials or reagents commonly used for research purposes without patents.

Finally, OTA asked if any potential licensees had declined to license a discovery because the firm objected to a domestic manufacturing preference clause. Five institutions have ever turned away an interested company for this reason, for a total of six scuttled deals in fiscal 1992. Four of those potential deals involved research funding from NIH, and none involved DOE-funded research. Almost all the institutions commented that they never had a need to end licensing discussions with a company over the issue of manufacturing in the United States, primarily because licensees manufacturing operations were domestic anyway.

As part of the data analysis, OTA analyzed a few cross tabulations. For example, to examine whether a correlation exists between high income and seeking licenses before filing for patents, licensing income data for both NIH and DOE were compared with data from questions about seeking licenses on discoveries prior to filing a patent application. Based on the data, no real difference exists in behavior between institutions, regardless of income. Some institutions with no license income always attempted to find licensees before patent filing. As well, no differences emerge when rates for successful licensing prior to patent filing. For NIH, all but one of the five institutions with high licensing income sought licensees before patent filing 50 percent or more of the time. However, of those institutions, one claimed success 50 percent of the time and four said they were successful 10 percent of the time or less. For DOE, 10 institutions had any income; the two institutions with more than \$200,000 reported success in licensing discoveries prior to patenting 20 percent of the time or less. Little can be said about the relationship between income and pursuing licensees before filing for patents.

Licensing income data for both NIH and DOE research were also crosstabulated with data from questions about the methods used to find potential licensees. Based on this analysis, OTA found no marketing technique unique to institutions that had high licensing income. All respondents use all marketing approaches to about the same extent, regardless licensing income. All but one institution reporting high income turned to key companies to try to license discoveries 75 percent or more of the time. Conversely, less than 20 percent of the time, all but one respondent reporting high income publishes discoveries in an electronic database to which potential licensees have access. For

institutions reporting high income, all remaining methods of finding potential licensees tend to be used less than 50 percent of the time.

In addition, licensing income data were compared with data from questions probing the effectiveness of certain methods of technology transfer, to determine if there is any correlation between levels of income at the institutions and the perceived effectiveness of those methods. Again, all methods of technology transfer are viewed as effective or not effective to the same extent by the institutions, regardless of income. All high income institutions viewed exclusive licensing as very effective, including the institutions reporting the highest income from nonexclusive licenses. The high income institutions were split on the effectiveness of nonexclusive licensing, just over half viewing it as effective and the remainder claimed it as very effective. One of the high income institutions felt that sponsored research agreements are an ineffective method of technology transfer. Direct investment in licensees was viewed as not effective by all but two of the high income institutions, which viewed it as a moderately effective method of technology transfer. Technical assistance, personnel exchange, site visits, and setting up spinoff companies were all claimed to be generally effective by institutions with high income. Institutions reporting little or no licensing income shared no coherent viewpoint on the effectiveness of these methods of transferring technology.

The same income data were compared with data from questions examining obstacles to technology transfer at these institutions, to determine if there is a simple correlation between the perceived obstacles at the institutions and their income. Once again, obstacles to technology transfer

were generally ranked at similar levels by all institutions regardless of income. The most significant obstacle overall according to the survey--unproven state of technology--is ranked as the second most severe obstacle to technology transfer by four of five institutions reporting notably high income, with one high income institution claiming it as the most significant obstacle. Conversely, a general lack of industry interest in technology transfer at academic institutions is the most serious obstacle for four of the five highest income institutions, with one of the five claiming it as the second most severe obstacle. For all obstacles however, the rankings tended to be similar regardless of income from licenses.

Finally, income data from the institutions were crosstabulated with patent filing and licensing data to determine whether a correlation exists between those institutions filing for and licensing patented discoveries and income. One of the five institutions reporting high income filed over 40 patent applications. However two institutions with little or no income also filed for at least 40 patents. Conversely, one institution reporting about \$13 million in licensing income from filed fewer than five patent applications. The number of licenses granted to companies followed the same pattern. Based on the survey, OTA found no correlation between tiling for patents or entering into licensing agreements and income from licenses. It is critical to note, however, that patents and licenses do not immediately yield income, usually not even in the same year that the patent issues or the licensing agreement is signed. Patents and licenses are among the first steps toward building a stream of royalty income derived from sales of a good or service that incorporates the technology invented in an academic research institution. Hence, the income reported by the institutions in this survey is primarily derived from patents and licenses in prior years.

Overall, then, OTA's survey found that the Bayh-Dole Act is vital to academic technology transfer. The ultimate degree of economic success--one of the motivating factors for the passage of Bayh-Dole and other technology transfer legislation--cannot be fully understood, however, because of the relative novelty of academic technology transfer related to genome research; its full economic value remains to be evaluated. Clearly, however, academic research institutions successfully transfer federally supported research for private sector development. Significant barriers to academic technology transfer, in particular, are generally not a function of government laws, or regulations. It is evident that, in 1980, Congress provided incentives for nonprofit research institutions to license federally funded research, simply by changing the rules of intellectual property ownership. This was a clear step toward the commercialization of federally supported research, that Congress accomplished without appropriating any major funds for a new program of R&D. The same can be said for the value of health benefits for those individuals treated by biomedical technologies originally supported by U.S. government funding at academic research institutions.

Cooperative Research and Development Agreements

As defined and authorized by FTTA, a Cooperative Research and Development Agreement (CRADA) is an agreement between one or more Federal laboratories and one or more nonFederal parties, under which the Government provides personnel, services, facilities, equipment, or other resources (but not funds), and the nonFederal parties provide funds, personnel, services, facilities, equipment, or other resources toward the conduct of specific research or development efforts (15

U.S.C. 3710a[d][1]). Under the CRADA these resources are provided toward the conduct of specified research or development efforts consistent with the missions of the laboratory.

CRADAs are one of several mechanisms for Federal laboratories to share research materials and data and collaborate on research with industry. CRADAs are intended to be agreements negotiated between individual laboratories or institutes and nonFederal parties, although there is oversight from Federal agencies. DOE laboratories have other arrangements for sharing facilities with industry, such as doing “reimbursable work for others,” and by providing access to unique laboratory facilities under a “user facilities” program. DOE CRADAs differ from other arrangements at DOE in that DOE has to share its resources with companies. In some cases, the companies come out of CRADAs with rights to keep laboratory notebooks, and information can be protected from general dissemination for up to 5 years (Blumenthal, 1993).

The number of NIH CRADAs grew from 39 in 1988 to 109 in 1993, including 16 in 1993 at the Centers for Disease Control (CDC) and 9 at the Food and Drug Administration (FDA). CRADAs at the CDC and FDA are reviewed under the NIH CRADA review process (Blumenthal, 1994). The number of new CRADAs appears to be tapering off to around 25 per year, having peaked at 114 in 1990 (Blumenthal, 1994). These numbers are approximate because they represent the number of CRADAs in existence at a single time point per year, which OTT publishes as an annual list (except for 1993, for which OTT provided OTA a list as of August 1993). Additionally, the number of CRADAs in the published lists differs from totals provided by OTT when it computed totals from

their database of CRADAs, and OTT has been unable to reconcile the differences between the two sources.

DOE CRADAs have grown at a faster pace over fewer years than NIH CRADAs. In April 1991, DOE had 12 CRADAs at its laboratories. As of July 1993, DOE CRADAs grew steadily to a total of 465 ongoing CRADAs, including 16 in biomedical research as of April 1993 (Blumenthal, 1994).

At NIH, OTT coordinates the approval process for CRADAs that include exclusive licensing, although CRADAs are agreements between the individual institutes and companies consistent with FTTA's emphasis on the decentralization of technology transfer. OTT has 45 employees, but none are devoted full time to CRADAs. Normally, around five percent of OTT's effort is devoted to CRADA issues (Blumenthal, 1994). The Division of Management Policy of NIH evaluated OTT, and out of that process has come a corrective action plan that calls for a total of 58 employees, two of whom would work full time on CRADA issues (Blumenthal, 1994). Institutionally, OTT reports to the Deputy Director for Science and Technology Transfer, who reports to the NIH Director.

DOE CRADAs are agreements between the contractors operating government owned laboratories and nonFederal parties, but DOE must approve each CRADA and exerts financial control over the government funding contributed to its CRADAs. The Department of Commerce, under FTTA, is responsible for advising and assisting other government agencies regarding CRADAs. However, because FTTA places major emphasis on the decentralization of the technology transfer process, the authority for entering into CRADAs is delegated to the directors of individual

institutes, centers and laboratories. However, the legislation provides for time-limited opportunities for review by officials at senior levels. DOE's technology transfer management has been delegated to its field offices, where CRADAs can be approved if they are not substantially different from the model (Hightower, 1993).

The Role of CRADAs

In general, CRADAs take a variety of forms, depending on the goals of the CRADA partners. Most Federal agencies, including DOE and NIH, have model CRADAs that are used as the basis for negotiation with potential collaborators. A model CRADA contains a statement of work, estimated funding contributions of both parties, terms regarding retainment of property, a product liability article, proprietary information, intellectual property and licensing requirements, and reporting requirements.

According to a recent survey, industry is primarily interested in accessing expertise and unique facilities at Federal laboratories (Roessner, 1993), and interest in forming CRADAs, with the DOE contractor-operated laboratories in particular, has increased in absolute terms. Most respondents to this survey held a positive view of the laboratories and consider them to be a unique R&D resource. And the purpose of entering into CRADAs or other collaborative relationships with the laboratories is less to license anything so developed, than to conduct research enabling further development (Roessner, 1993).

Access to NIH expertise, research tools, and scientific capabilities usually takes the form of CRADAs. According to OTT officials, NIH generally does not enter into work for others or into sponsored research agreements, in part to avoid the perception that NIH is trying to justify its usefulness by soliciting outside projects and research topics (Adler, 1993). The CRADA review process at NIH is not centralized, though OTT officials believe that it should be centralized under OTT authority. Indeed, OTT claims that firms prefer a centralized CRADA review process because it would be smoother and simpler than the process currently in place (Adler, 1993). At present, OTT submits CRADAs to the Office of General Counsel at the Department of Health and Human Services (DHHS) for final review.

Access to national laboratory expertise, research tools, and scientific capabilities frequently takes the form of CRADAs. According to DOE officials, however, the national laboratories generally negotiate thousands of work for others agreements annually, under which smaller scale collaborative R&D is performed (Hightower, 1993). In 1993, 342 new CRADAs with non-Federal partners were approved by DOE (Birely, 1994).

In general, CRADAs present both NIH and DOE with opportunities to gain from collaboration with industry. According to recent reports from DHHS' Inspector General, most NIH investigators stressed that industry partners made substantial contributions to the collaborative research that would not have been available otherwise (U.S. DHHS, 1993). According to one NIH CRADA administrator, many CRADA companies contribute up to \$150,000 per year into the collaborative research (Blumenthal, 1994). CRADAs present industry with the opportunity to access

discoveries that have been made in NIH and DOE laboratories and pursue further development. If the discovery is a human DNA sequence of undetermined function, then a CRADA might be an appropriate vehicle for collaborative research to isolate the protein encoded by the sequence. The key element of CRADAs seems to be exclusive patent rights, which is negotiated in advance.

Forming and Administering CRADAs

Two types of NIH CRADAs exist: extramural CRADAs, in which companies collaborate with NIH scientists to test medical technologies, and intramural CRADAs, in which companies collaborate on basic research with NIH scientists. The companies develop applications, and the CRADA secures both parties' rights. Intramural CRADAs originate in a number of ways. An institute may initiate a CRADA for development and application of the institute's patented invention. The institute may initiate multiple CRADAs, each for a different delivery system. In such cases, the Institute or agency will generally advertise its interest in forming a CRADA through the Federal Register and other means. An example: Scientists at the NIAID developed a vaccine for the sexually transmitted disease chlamydia, and NIH patented it. The Technology Development Coordinator for NIAID then sought bids for development of a delivery system for the vaccine. Three bids were found to have scientific merit and CRADAs were established.

CRADAs may also be investigator-initiated, beginning with contacts between company and NIH investigators at scientific meetings. In such investigator initiated arrangements, the company

may collaborate with the institute on anything from the most basic preclinical research through the development of a product for public distribution and sale.

Companies may also originate CRADAs. To stimulate industrial initiatives, NIH recently convened science fairs for firms, displaying the work of its intramural researches in the hope of stimulating industrial overtures. OTT also annually publishes the PHS Technology Transfer Directory, which lists PHS investigators interested in considering research collaborations with industry cross-referenced with their areas of research.

CRADAs may run up to four years in duration, plus a one-year extension. According to one CRADA administrator, many companies with a CRADA put funds of up to \$150,000 per year into the CRADAs, but for other CRADAs the corporate funding is minimal, perhaps covering travel to conferences for a Federal scientist or compensation for a postdoctoral fellow (Blumenthal, 1994).

To protect the academic value of the research conducted at the Federal laboratory, the U.S. government agency insists that the Federal investigator make an intellectual contribution to the joint work as part of the CRADA. The purpose of this requirement is to insure that firms will not use CRADAs to do the kind of work they could do in their own labs, and that intramural facilities will continue to conduct research that makes a fundamental contribution to scientific knowledge.

Since DOE intramural labs are generally government-owned and contractor operated (GOCO), DOE CRADAs take the form of a contract between the contractor operating the laboratory, and a company. The Federal government is not a signatory, but it retains nonexclusive paid-up

royalty-free worldwide rights to CRADA inventions and discoveries, including the right to have products manufactured by another company for the government's use.

A GOCO laboratory's contribution to a CRADA must be funded in a way that has been approved by DOE. DOE's Energy Research (ER) program and the Defense Program (DP) have allocated funds that are reserved for the government's part of the CRADA contribution, and most DOE laboratory life science CRADAs are within these two programs. Some DP laboratories--Y 12 at Oak Ridge, Sandia, Los Alamos, Lawrence Livermore--participate in a process to determine jointly the priorities among proposed CRADAs for allocation of their CRADA funding (Blumenthal, 1994). DP CRADAs are required to be "dual use" CRADAs--i.e., demonstrate both a defense-related and a nondefense-related use for the research.

ER CRADAs are generally funded on the laboratory side by block funding, where DOE pays the laboratory a block amount for a specified set of deliverables. The laboratory then must find a company that might want a CRADA, referred to as a spin-off CRADA (Blumenthal, 1994). One benefit of having laboratories seek corporate CRADA partners, rather than the reverse, is that the companies may become involved at an earlier stage of the research. Thus, the risk that a research project might not lead to a useful result is shared between the public and private sectors at an earlier stage--i.e., there is earlier leveraging of the public investment in research.

At NIH, an administrator, known as the Technology Development Coordinator (TDC), plays a central role in managing the development and approval of CRADAs. TDCs generally become involved when they are approached by intramural scientists or company representatives, though on

some occasions TDCs have suggested CRADAs themselves (Blumenthal, 1994). Once the process is initiated, TDCs advise the intramural scientists on a research plan and developing a CRADA application according to the model agreement.

If a provision for exclusive licensing is included in the proposed agreement, the CRADA Subcommittee of the NIH Patent Policy Board must approve the application. The Patent Policy Board is now defunct, but its Subcommittee still exists and functions as the primary body for reviewing CRADAs prior to their formal approval, answering to the Technology Transfer Policy Board. A successful CRADA typically takes 11 months to clear this review process (Blumenthal, 1994). The CRADA Subcommittee makes recommendations to the NIH Director and to the institutes or centers.

If review by the CRADA Subcommittee is required, OTT also conducts a legal review of the proposed CRADA. Most CRADAs provide for exclusive licensing, and even when they do not, the CRADA Subcommittee often reviews them (Blumenthal, 1994). It does not seem to be common knowledge that a CRADA that without an exclusive licensing provision may escape Subcommittee review.

The CRADA Subcommittee review employs a two-stage process. The first stage involves a preliminary review by the relevant institute's TDC, the Office of the General Counsel, and about five other TDCs; the NIH scientist does not participate. In the second stage, the scientist discusses the science and research of the proposed CRADA before the Subcommittee. Following the second review, the research plan might be adjusted or modified, which requires a third review before the

CRADA Subcommittee. Scientists and companies who have participated in this multistage review note that during the second and third reviews issues are sometimes raised that could have been raised and resolved during the first stage (U.S. DHHS, 1993); in some cases, this situation arises because the Subcommittee's membership has changed or because members who could not attend the initial review attend a subsequent session (Blumenthal, 1994). The CRADA Subcommittee may decide, however, that required modifications are sufficiently minor, approving the CRADA on condition of specified modification. If adjustments are needed, the TDC interacts informally with the scientists, the company, and possibly members of the Subcommittee to bring the application into conformity with the Subcommittee's requirements (Blumenthal, 1994).

The CRADA Subcommittee pays particular attention to defining the CRADA's scope because anything in the scope of the research plan may be amenable to exclusive licensing by the company. NIH officials believe that it would not be in the public interest for a single company to tie up a large area of research (Blumenthal, 1994). Further, a well-defined scope helps ensure that a proposed effort does not overlap rights already ceded to another company in a different CRADA. Another check to prevent against overlap centers on requirement that both NIH scientist(s) and company scientist(s) contribute intellectually; companies may not simply buy up interesting research from a laboratory. Other topics reviewed include issues of fair access by other firms to the potential CRADA and preference for U.S. firms (Blumenthal, 1994).

Like NIH CRADAs, staff of each DOE laboratory's technology transfer office assist companies and the GOCO laboratory's scientist in developing CRADA applications; DO. A model

CRADA form was developed by DOE in 1989 (Hightower, 1993). It usually takes six to eight months to get funding for the government share of the DP CRADA, then it is an additional six months for DOE to approve the CRADA. There is an annual call for proposals and an elaborate selection process among 4 laboratories--Y12 at Oak Ridge, Sandia, Los Alamos, and Lawrence Livermore. Representatives from each laboratory rank proposed CRADAs, which go as recommendations to the Office of Research and Technology Applications (ORTA) heads for a further recommendation (Blumenthal, 1994). The final approval must come from DP headquarters. Since the average time to fund and approve a CRADA is over a year, and the call for proposals once a year, almost two years can lapse from a project's conception to approval. Representatives of the laboratories say they have seen potential corporate CRADA partners give up and walk away from the process (Blumenthal, 1994).

The ER block funding arrangement obviates the 6- to 8-month first step of the DP CRADA approval process, because the approval and funding for the project has already been approved before the CRADA is initiated. Even so, each CRADA still must be approved by the DOE at headquarters or a field office (Hightower, 1993):

The Outlook for CRADAs

In 1993, the DHHS Inspector General found that CRADAs offer several benefits to both NIH researchers and industry scientists, including pooling of intellectual and financial resources, research materials, equipment, and facilities. A CRADA generally allows for the establishment upfront of the

rights of both parties to the CRADA, which lets NIH scientists focus on their research (U.S. DHHS, 1993). Still, the report also found several shortcomings of CRADAs at NIH.

- Many CRADA projects may not be suited for the CRADA mechanism because they do not focus on the transfer of technology from Federal laboratories to the private sector.
- The process of establishing CRADAs is lengthy and complex, discouraging industry participation in CRADAs.
- Many NIH and industry investigators consider the CRADA formation process to be inefficient and a disincentive to further participation in the CRADA program.
- NIH does not have guidance that adequately addresses the problems of providing fair access for parties interested in CRADAs.
- Limited NIH oversight of CRADA projects might inhibit the ability of NIH to ensure that CRADAs are consistent with the goals of FTTA.
- Pricing of CRADA products is a matter of considerable controversy that reflects the difficulty of striking a balance between protecting the public investment in research and maintaining industry's incentive to collaborate through CRADAs (U.S. DHHS, 1993).

PHS agreed with all of the findings except the first, claiming that no inconsistency exists between the intended and current uses of CRADAs. PHS claimed there was “no indication that it was the intention of Congress to limit CRADAs only to research that reflects practical technology rather than to generally encourage mission-appropriate research (U.S. DHHS, 1993). In response to the other findings, PHS initiated several programs at NIH attempting to rectify the problems, with a schedule for their resolution. Despite these ongoing efforts, issues of fair access, the drug pricing

controversy, and international trade agreements could still undermine the future of CRADA programs at NIH (Hanna, 1994).

Fair access in CRADA formation is an issue for which Federal agencies, including NIH and DOE, remain vulnerable. NIH meets this requirement on an ad hoc basis. Scientists and TDCs say that generally the scientists know all the firms who are working in their field and know who would be best to work with. Further, they say it is important that NIH scientists be permitted to work with industry scientists with whom they are comfortable working (Blumenthal, 1994). Yet, if all capable firms are not given the opportunity to form a CRADA, then the CRADA research might not improve health care as much or as fast as possible. Also, capable firms might not attempt to form CRADAs if they feel disadvantaged by the politics of the CRADA partner selection process. In the extreme, once a product is brought to market, a firm could bring a lawsuit charging that it was unfairly denied access to the CRADA process. All in all, there is good reason for the CRADA Subcommittee to pay careful attention to fair access issues in its review of CRADA proposals.

As noted earlier, the pricing of drugs is an issue of considerable policy controversy, but there is a standard “reasonable pricing” clause in the model CRADA agreement that is used consistently. Further, PHS has instructed NIH that it may not vary at all from the model CRADA on the subject of reasonable pricing (Blumenthal, 1994). The wording of the reasonable pricing provision, developed several years ago through discussions of the director of OTT with the Patent Policy Board and the General Counsel’s Office, is:

“NIH/ADAMHA have a concern that there be a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety

needs of the public. Accordingly, exclusive commercialization licenses granted for NIH/ADAMHA intellectual property rights may require that this relationship be supported by reasonable evidence” (Blumenthal, 1994).

The formation of new CRADAs at NIH has been chilled by industry’s fear that prices will be set or manipulated by NIH or the DHHS. Some industry representatives claim that at NIH, the pricing controversy has significantly retarded the formation of new CRADAs (Washington Fax, 1993). Indeed, a recent OTA workshop attended by industry representatives pointed out that their interest in CRADAs has been significantly retarded by recent discussions concerning price controls on pharmaceuticals (Shapiro, 1994).

Results of a Survey of U.S. Biomedical Companies

To understand CRADAs from the perspective of companies that have or potentially could have collaborative research relationships with NIH and DOE (life sciences only), OTA conducted a survey of 100 biotechnology companies in late 1993 and early 1994. A sample of firms, with and without life science CRADAs at DOE or NIH, was drawn and survey questions focused on the value to companies of CRADA collaborations, as well as the nature of the collaboration between the companies and Federal laboratories. A total of 68 companies qualified following initial screening and responded to both written questionnaires and telephone interviews. The survey questions were asked of the vice-president for R&D, or other comparable executive for each company.

The demographic characteristics of the survey sample emphasize the scale and scope of the types of companies that the FTTA legislation setting up CRADAs was intended to assist. Of 68

responding companies, 8 are subsidiaries of other companies, and 4 are divisions of larger companies. These companies responded with data drawn from the parent company. The average estimated gross revenues for the current fiscal year at the 68 companies is expected to be \$990 million, with a projected average life sciences R&D budget of \$30 million this year, and the 68 respondents employ 848,063 employees. Over the past five years, respondents received 1,223 patents from PTO, and expect expected total of \$1,705 in royalty revenues from discoveries licensed to other parties in the current fiscal year. The 68 companies have a combined total of 1,957 health care products on the market at present, 1,168 (60 percent) of which required regulatory approval.

The survey data provide some general indicators of the value to respondents of research performed under CRADAs. Of the 68 companies, 18 reported having CRADAs with NIH and 9 reported having CRADAs with DOE (35.3 percent). Three of the 27 companies had both NIH and DOE CRADAs, and 24 companies had CRADAs with either NIH or DOE. CRADAs undertaken by the OTA survey population led to 17 patent filings and 16 issued patents over the past five years, though to date only two are life science products. The companies reported to OTA that, on average for the 24 firms, 2.2 percent of gross revenues for the past five years resulted from research performed under CRADAs, totaling just over \$31 million for the past five years. For these companies over the past five years, royalty income from licenses to which the CRADA contributed were insignificant. These data imply that CRADAs have yet to create much value for the firms that enter into life science CRADA partnerships with NIH and DOE.

The survey also probed the experiences of the companies with life science CRADAs at NIH and DOE. Of 68 companies, 18 reported having experience with a total of 31 CRADAs at NIH, including ongoing and terminated CRADAs. And 9 companies reported having 13 life science CRADAs with DOE, including terminated and ongoing CRADAs. The 3 companies with both NIH and DOE life science CRADAs were asked if there was any difference between CRADAs at NIH and DOE. One of the companies claimed there was no difference and two others claimed there was a significant difference.

To further detail companies' experiences with CRADAs, one CRADA was randomly selected from a list a respondent provided. Among the issues explored were the extent of the companies' and NIH or DOE laboratories' contributions. For the 24 companies with CRADAs at either NIH or DOE:

- 14 companies reported that Federal researchers were provided to explore topics of interest to the companies;
- 15 companies reported that their laboratories were provided with U.S. government materials and equipment;
- 8 companies had access to equipment in Federal laboratories;
- 13 companies had exclusive licensing provisions in the CRADA agreement;
- 3 companies received exclusive licensing privileges to research that was not conducted under the CRADA;
- 7 companies provided researchers to work in Federal laboratories;
- 18 companies provided materials and equipment;

- 8 companies provided access to their equipment for Federal researchers;
- 11 companies provided compensation for Federal researchers;
- 13 companies provided other funding for Federal researchers;
- 10 companies provided funding for, or otherwise conducted the patent application process;

Clearly, Federal laboratories contribute a share of resources to CRADAs, but OTA data reveal that a company's contribution to the CRADA is not insignificant. To the extent that companies share the burden of CRADAs, it becomes more difficult to argue that they are getting a free ride from the U.S. government.

The data show that for the companies willing to invest in life science CRADAs at NIH or DOE, in most cases it is likely that U.S. government contributions (other than funds) will match those of the companies. Overall, 6 companies felt that the benefits greatly outweigh the risks and expenses of CRADAs, 6 felt the benefits somewhat outweighed the risks, and 9 thought the benefits equaled the risks and expenses. There were 3 companies that felt the risks and expenses of CRADAs greatly exceeded the benefits.

There are a number of concerns that trouble some companies participating in the survey, according to the data. Four companies reported that these concerns caused them to forgo or retreat from a CRADA with NIH or DOE. Eleven companies felt no concern over the possibility of disclosure of information that they had intended to keep secret. Six companies felt it was a major concern, and 7 felt it was a minor concern. Only two companies had major concern about

government scientists, involved under their CRADA, going to work for a competitor. It was a minor concern for 10 other companies. Eleven companies had major concerns that the reasonable pricing clause in the CRADA would restrict profitability of anticipated or unanticipated products resulting from the CRADA. Eight other companies felt this to be a minor concern, and six others had no such concerns. Six of the companies felt it was a major concern that the CRADA language had no guarantee of an exclusive license for unanticipated products developed under the CRADA, and eleven others felt it to be a concern of minor proportions. Of the 24 CRADA firms, 6 companies had major worries that the government would not honor the terms of the CRADA regarding exclusivity, and 7 other firms had similar but minor concerns.

From a qualitative viewpoint, the survey data from the 24 companies' randomly selected CRADA tended to endorse the general value of CRADAs. For example, 8 companies said that the intellectual contributions of Federal researchers were very important, another 12 claimed the contributions to be somewhat important. 14 companies felt that government researchers had contributed original research ideas unavailable without the CRADA. Moreover, 16 companies reported that the researchers technical know-how also would have been unavailable without the CRADA, and 16 companies expect an ongoing working relationship with the government CRADA scientists. Nine of these companies intend to pursue another CRADA, and the remaining 7 companies expect informal working relationships. A total of 15 companies felt that use of biological materials provided by the Federal laboratory was somewhat or very important, and 10 felt that the use of such materials and expenses would be unavailable outside the CRADA. When asked if they would do it over again for all of their CRADAs, 7 companies said that they would do so for all their

CRADAs, 8 said they would for most of their CRADAs, 3 said they would for some of their CRADAs, and 6 companies said they would be willing to repeat the experience for only few or none of their CRADAs.

Another set of questions probed the CRADA formation process from the companies' perspective. Seventeen of the firms, discovered the CRADA process via personal contacts, one reported reading a journal article, one firm was made aware of CRADAs at a professional meeting, 3 companies reported receiving promotional materials from the U.S. government. According to these data, personal contacts are most effective for forming life science CRADAs at NIH or DOE. Four companies claim that initial discussions toward forming CRADAs were begun by company officials, and 6 report that the discussions were begun by government officials. Thirteen companies claim that discussions began by both Federal and company officials equally. Within 16 of the companies, the research scientists themselves are the most enthusiastic advocates of CRADAs, and in 4 firms it was the vice-president for R&D. Efforts to make industry more aware of CRADAs are seen as very effective by 5 companies, somewhat effective by 10 companies, somewhat ineffective by 7 companies, and very ineffective by one other company. These data suggest that industry outreach could be improved on the part of Federal laboratories.

Relative to applying for life science CRADAs at NIH and DOE, 17 companies said they used a model CRADA application. Eight of these 17 companies thought it was generally helpful, 3 said it was neither helpful nor obstructive, and 5 firms felt it was obstructive. Nine companies felt that the government's involvement in writing the CRADA application was very helpful, and 5 other firms felt

it was somewhat helpful. Four companies claimed that Federal involvement is neither helpful nor obstructive, and 6 companies felt it was obstructive. Twenty of the companies said there was a Federal official responsible for coordinating the CRADA application process. For those 3 firms that said there was no such official, they all claimed it would have been helpful if there was a government coordinator. Only two companies felt that such an official neither helped nor obstructed, 18 firms felt that a coordinating official in the application process helped them. Fourteen companies reported that their application was reviewed by a committee, 6 firms claimed that the committee's review took longer than was reasonable. Three companies felt that the committee pointed out ambiguities or problems important to resolve.

Companies tend to focus on exclusive licensing of results to their CRADAs. Eighteen companies sought exclusive licensing in the CRADA application for patents that might result from the CRADAs. Concerning the scope of exclusive licenses in the application, 13 companies reported that it was an issue for negotiation. Five companies sought exclusive licenses to government held patents on material used under the CRADA, but not a result of it. However, 18 companies did not actually receive exclusive licenses from the government, despite 13 companies having exclusive licensing provisions in the agreement. Six companies did obtain exclusive licenses to their CRADA results. Apparently, some of the CRADAs did not result in anything worth licensing exclusively from the companies' perspective, or the Federal laboratory did not honor its agreements.

For those companies without any experience with CRADAs, a number of questions probed the nature of their attitudes and awareness relative to CRADAs. Fourteen of 33 companies had never

heard of CRADAs. For the 19 firms that were aware of CRADAs, 16 said they would consider entering into one. Ten of the firms aware of CRADAs had some contact with Federal officials or scientists concerning CRADAs, and for just two of these companies the contacts are still ongoing. Four companies said that it would be very likely that they would apply for life science CRADAs in the future, 8 said it would be somewhat likely that they would do so. A total of 17 companies said they would probably not be interested in life science CRADAs with NIH or DOE laboratories.

As part of the survey, OTA took the opportunity to inquire about relations between the survey respondents and foreign nonprofit research institutions, with a focus on intellectual property rights resulting from international R&D collaborations. According to the survey, 25 of the 68 companies claimed to participate in collaborative R&D agreements with foreign nonprofit research institutions complete with rights to intellectual property licensed or otherwise obtained from foreign research institutions, indicating the openness of at least 37 percent of the companies to international research collaboration. Only one firm claimed to have licensed technology from a U.S. party that had such rights originally based on an international research collaboration.

In summary, the data show the unevenness of the CRADA experience from the companies' perspective. Although most of the companies with CRADA experiences felt the Federal laboratory helped them, the fact that most firms did not obtain exclusive licenses to CRADA results belies the more enabling nature of the collaboration. In many cases, such a result is not necessarily a problem, but it does point to the likelihood of companies' expectations going unfulfilled. Further research on life science CRADAs needs to be done to confirm this point. From the U.S. government's

perspective CRADAs assist Federal investigators in many cases. This is consistent with the findings from the DHHS Inspector General's investigation (U.S. DHHS, 1993).

SUMMARY AND CONCLUSIONS

When NIH filed patent applications on EST fragments in 1991, one policy issue centered on the role of technology transfer between a Federal laboratory and the private sector. In the broader context of the Human Genome Project, however, the importance of technology transfer based on federally funded research at universities and research institutions probably surpasses this. Regardless, Congress enacted legislation to address technology transfer in both contexts through the Stevenson-Wydler and Bayh-Dole Acts of 1980. These laws do not operate on Federal technology transfer in a vacuum, however. Other laws and Federal policies, as well as controversies over the extent of Federal control over commercial sale of results of technology transfer affect this process.

OTA surveys of technology transfer offices at university and research institutions and of biotechnology companies reveal several findings. Nonprofit research institutions are beginning to become productive in transferring technology derived from research supported by NIH and DOE. NIH extramural funding has been more productive, in terms of measurable income, for academic research institutions than DOE life sciences research funding. Comparatively, Bayh-Dole has had more of an economically measurable effect than FTTA to date. For many companies, the technology transfer process employed by NIH and DOE laboratories, particularly through CRADAs, is frequently cited as a disincentive to enter into collaborative arrangements. Life science CRADAs

have yet to become economically productive for most companies that have CRADA experiences, according to OTA survey data.

Technology transfer involves many component processes arranged toward the goal of innovation. Innovation is not synonymous with invention, but requires financing and entrepreneurship to bring an invention to market. It is difficult to apply an already existing invention or discovery to some demand in the marketplace, even if the U.S. government has underwritten the process with public funds.

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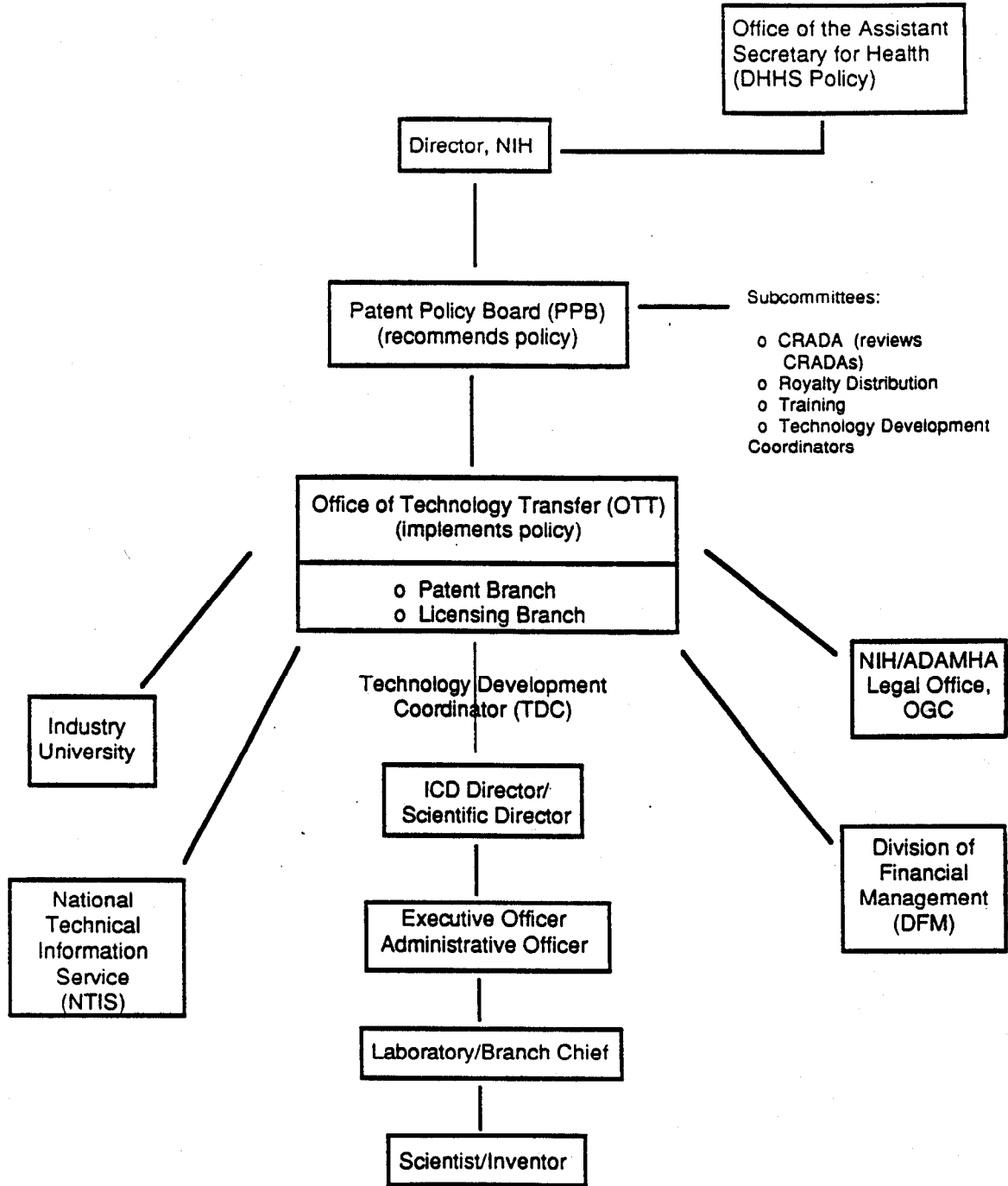
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Figure 6-1--Federal Technology Transfer Act of 1986: NIH Implementation



Box 6-A--Washington University-Monsanto Sponsored Research Agreement

Sponsored research agreements present both the corporate sponsor and the research institution with an opportunity to benefit. The key to taking advantage of this opportunity is ensuring that care is taken in the process of reconciling the profit maximizing goals of the corporation with the academic mission of the nonprofit research institution. Moreover, the concerns of the U.S. government must be considered as well, because of significant Federal support for biomedical research at nonprofit research institutions. The reconciliation of these separate institutional goals must be accomplished in advance through negotiations, with care taken to include the concerns of all three institutions in the deliberations, especially if the proposed agreement is very large. Most sponsored research agreements are small and easily managed by all parties involved.

Some agreements, however, are broader, for longer periods of time, and involve much greater sums of money. For example, at Washington University, Monsanto is providing about \$9 million each year on topics chosen by the research faculty which are of interest to Monsanto as well (Cullen, 1993). Monsanto funding represents five percent of the annual research budget at Washington University, and Monsanto is restricted to research on bioactive proteins and peptides under the agreement (Cullen, 1993). Monsanto issues requests for proposals (RFPs) each year, describing areas of specific interest that faculty members may submit proposals for. Proposals are reviewed by a joint committee of five senior scientists from Monsanto and five from Washington University. Every two years an independent audit of scientific quality is conducted, the most recent of which was performed by several members of the National Academy of Sciences (Cullen, 1993). Under the

agreement, faculty members agree to assign their patents to Monsanto and to keep confidential any proprietary information they receive from Monsanto. Manuscripts are reviewed and then released for publication in 30 days or less. There are no inhibitions on collaboration with faculty at other institutions, and a mechanism exists for sharing research materials based on Monsanto funded work (Cullen, 1993). On occasion, a patentable discovery has been developed with funding from Monsanto and the U.S. government. In such cases, the provisions of Federal law are applied to the discovery, including the Bayh-Dole Act (Cullen, 1993).

Some experts express concerns about sponsored research agreements, particularly those which are large in scale or scope. Among the concerns are: agreements excluding rival firms from access to unused R&D, deals allowing companies to excessively control the direction of research and its results, and provisions that restrict the freedom of researchers to publish their work. In the wake of the controversy over the proposed agreement between Scripps Research Institute and Sandoz Pharmaceutical, NIH conducted a survey of 375 sponsored research agreements at 100 U.S. research institutions. The survey revealed that most agreements are small and of little cause for concern. Indeed, according to NIH officials, there were no agreements similar to the Scripps-Sandoz agreement (Macilwain, 1994). Nevertheless, in response to a congressional directive, NIH is currently drafting guidelines to resolve concerns about the potential for sponsored research agreements and a perceived abuse of Federal funding at nonprofit research institutions.

SOURCE: Office of Technology Assessment, 1994.