ARTICLE

Patents and Research—An Uneasy Alliance

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ABSTRACT

Critics of the patent system have argued that rather than promoting the progress of science and the useful arts, the patent system as it exists in the United States and perhaps elsewhere may actually inhibit such progress. Much of the criticism has been focused on patenting of research tools. The author attempts to evaluate the extent of this effect, and to suggest some possible modifications to the patent system to address its shortcomings. She considers the advantages attributed to the patenting system—providing incentives for finance and development and spurring creativity—with the disadvantages perceived by the academic community, including impediments to the communication of research findings and other transaction costs. Also examined are possible options for mitigating these problems, including legislative restrictions of certain subject matter from patentability, or strengthening the criteria used in review of patent applications, especially non-obviousness and utility. In addition, the author discusses potential "post-patent solutions," such as legislative or other restrictions on licensing.

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Critics of the patent system have for some time argued that rather than promoting the progress of science and the useful arts, the patent system as it exists in the United States and perhaps elsewhere may actually inhibit such progress. Much of the criticism has been focused on patenting of research tools. This is said to inhibit the access of those attempting to advance science and technology to the necessary means for achieving these goals. This paper attempts to evaluate the extent of this effect, and to suggest some possible modifications to the patent system to address its shortcomings.

BACKGROUND AND RATIONALE

When Article I, Section 8, of the U.S. Constitution was drafted to include, among the powers of Congress, the power to "promote the progress of science and useful arts by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries," it was a very different world. The inventions and discoveries were in the nature of bifocals, lightning rods, and other clearly practical articles of the type we might associate with the work of independent inventors today. The science of chemistry was barely off the ground, and the basics of organic chemistry (which laid the foundation for much progress in the just-concluded 20th century) were still a century away. There were no large research establishments either private or public, the very establishments that need funds to employ people who spend 100% of their time doing research. Even in 1952, the last time the patent statute was globally revised, the formalized research establishment was much in its infancy. Perhaps a major exception was the pharmaceutical industry, which even then relied on intense effort to discover new chemical entities that could be used as drugs. Ironically, the pharmaceutical industry has been one of the most successful exploiters of the patent system, and it is easy to see why. By assuring exclusivity to the industry's products, the patent system assures that sufficient funds can be generated to maintain the in-house research establishment, and assures each company that its expenditures in development to bring a new drug to market will not be wasted by immediate competition from generics. The patent system seems ideally designed for the pharmaceutical industry for this reason—at least until now.

By and large, the system does not appear to work so well when it comes to protection for products that are useful as "research tools" rather than consumer end products. The

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costs of doing research may become prohibitive if patentees of research tools take full advantage of their exclusivity. It might all be very well to assert that research tools simply should not be patented, but in the context of the present extensive research establishment, these are commercial products as well. Companies such as Stratagene, Beckman-Coulter, Invitrogen, and a multiplicity of others are in the business of making and supplying research tools. They want to make a profit, too.

If there are complaints, such as those above, that the patent system does not serve the purposes of the research community very well, this should be no surprise. There was essentially no research community at the time the system was devised. And, exclusivity as the reward for innovation (rather than direct monetary compensation from the government, for example) was appropriate. An alternative scheme of direct compensation today seems so far from public consciousness that there is hardly any point proposing it. It exists only in the context of the government's providing funds to enable a limited number of researchers to do their work, essentially independently of whether anything new, useful, and non-obvious comes out of it.[1]

THE NATURE OF THE "PROBLEM"

What are the advantages and disadvantages of applying the patent system in the context of a large research community, which includes universities, private foundations, government institutions, hospitals, and commercial institutions?[2]

Putative advantages include incentives to finance an extensive research establishment in order to provide a pipeline of potentially patentable products, incentive to incur development costs for patented products, and encouragement of individual researchers to develop new and useful processes and products (provided there is a mechanism for the individual to reap the financial benefits). Disadvantages include a deterioration in the open exchange of information, extremely high transactional costs, and inhibition of the most efficient ways to actually conduct research. And, depending on one's viewpoint, the asserted advantage of encouraging development of new and useful subject matter may be considered a detriment by discouraging more basic research.[3]

INFORMATION EXCHANGE

Taking a look at the disadvantages individually, it seems fair to conclude that an open exchange of information is, at least to some extent, inhibited by the availability of patent protection. It is not so clear whether this is a function of the patent system per se or of the growing tendency of research to become commercialized in general. As long as scientists were content to spend their time in the laboratory satisfying scientific curiosity in return for simply being provided a livelihood, the only incentive to remain quiet about progress in research was fear of being scooped by a colleague/competitor. But when it became apparent that money could be made if one's inventions and discoveries were commercialized, the necessity to maintain exclusivity (through the patent system) became paramount. This restriction on communication may arise either at the individual researcher level, for example at a university where the inventor on a licensed patent will be provided a large percentage of the proceeds to the university, or at an institutional level where a commercial enterprise has an interest in assuring that its employees do not undermine exclusivity (patentability) of inventions made on company time. Just as in the situation where the impediment was a fear of being scooped, there is a time limit on this reluctance, since once a patent application is filed, if it is to be pursued it will be published in any event in 18 months.[4] And it is by no means clear that there is greater reticence of disclosure when patents loom on the horizon than there is when researchers are simply trying to win the race to the goal.

Most license agreements and collaboration agreements provide for a review period prior to publication of any research results so that a patent application can be filed if desired. Typically, these review periods are of the order of 60–90 days. Most universities will not agree to a provision whereby publication after that is prevented; thus, once the application is filed or permission is given, whichever is earlier, the researcher may proceed with publication.[5]

TRANSACTIONAL COSTS

Transactional costs constitute a clear disadvantage of this system. First, there is a recognized massive transactional cost associated with the exchange of research materials. Everyone who supplies a material to another researcher wants to make sure that any inventions that are made somehow reflect the contribution of the materials supplied. This has spawned a cottage industry of drafting and negotiating Material Transfer Agreements (MTAs) between educational institutions, educational institutions and government, educational institutions or government and industry, and on and on. Gone are the days, if they ever existed, where it would simply be possible to write to a colleague asking for a sample of a compound described in a publication, or to request a cell line or other research tool, and have the recipient simply send the material off in the mail.[6] Typically, MTAs place constraints on what the recipient can do with the material, require review of publications that involve the material, and require indemnification of the sender by the recipient in case anything goes wrong. They may also contain other obligations to which the recipient might rightfully object, such as in-

sisting that any inventions made with the material become the property of the sender, not the inventor. The experience with these agreements has been terrible. At one point, the National Institutes of Health (NIH) attempted to standardize such agreements so that the expense of drafting them and securing their execution could be minimized. These standard agreements do not seem to have been widely adopted. Complaints are registered all the time about delays in transfer of requested materials and the expense required of institutions to set these formalities in motion.

Another serious transactional cost is in securing patent protection itself. The costs can vary widely, but even if the costs of drafting and prosecuting the application are discounted (i.e., the service fees charged by law firms or the costs incurred by companies or universities to provide an in-house patent department), the filing fees, at least outside the United States, are substantial.[7] Maintaining a reasonably extensive patent portfolio on a single application for the life of the patent can easily amount to several hundred thousand dollars. If there is more than one invention involved, which of course one hopes there would be for any prosperous entity, the "patent budget" will be large. Current estimates are that a research-oriented entity would allocate approximately 2–5% of its research costs to maintaining its patent estate. And that is assuming that everything goes well. If there is difficulty in obtaining grant of the patent, thousands of additional dollars may be spent. And because the United States maintains its first-to-invent system, should there be a competing application, an "interference" proceeding to sort this out can run close to a million dollars.[8]

This is not all. Because of the ubiquitous nature of the desire to acquire patents, it is more often than not the case that the business plan of a new enterprise is impacted by the existence of patents of others. Several tens of thousands of dollars are generally required to undertake "due diligence" to discover whether the enterprise has "freedom to operate" to carry out its own research and business plans. This is a major factor in its obtaining funds. If problematic patents are found, additional transactional costs are incurred in obtaining licenses to these.

In short, as might be expected, the patent system is itself a factor in the economy and consumes resources that might be spent elsewhere, such as in doing the research in the first place. Patent agents and attorneys are themselves required to have technical backgrounds (as is logical), and these then are people who are not doing the science for which they are trained, but simply supplying the superstructure.

INHIBITION OF RESEARCH

There is also the issue of inhibition of research per se. A perusal of the catalogue of a research tool supplier will verify that a reasonable percentage of the research tools offered, when sold to commercial institutions, require the commercial institutions to obtain licenses from the patentees. This is over and above the fact that presumably the price of the materials already includes a factor for paying a royalty to the patentee based on the sale of the goods. Sales are not required by law to be unconditional, and if made conditional (as they are), they do not exhaust the patentee's rights. Further extraction of funds can be had from the buyer. This has had some inhibiting effect.

Experience has shown that although buyers might be willing to pay some kind of reasonable fee for the use of the purchased material for commercial purposes, the requests by the patentees are often exorbitant—approaching $1–2 million in some instances.[9] This simply prices these tools out of the market, and the researcher is instructed to find some other way to do the experiment. Obviously this is not the most efficient way to conduct research.

The worst case, of course, is that wherein the patentee simply refuses to grant a license at all, which, under U.S. law, the patentee is perfectly entitled to do for any reason or no reason. The only exception is for the government as the user of the patented subject matter; the government has essentially a right of eminent domain.[10] There is always the right of the government to practice an invention for its own interests; its only obligation is to pay a fair royalty.

The problem is compounded if there are multiple patent holders whose claims would be infringed by carrying out the research. This might occur, for example, if the goal is to discover a drug for the treatment of a disease mediated by an identified receptor. There may be patent claims to the receptor itself, to the nucleotide sequence encoding it and means for its production, to cell lines that produce the receptor, to methods of screening using the receptor, to various cell lines that are useful in confirming the results obtained from the screen, to antibodies to the receptor needed to purify it, and so on. In some instances, more than one patentee will hold such claims. Further, as is discussed later, because of the flurry of sequencing activities, it is at least theoretically possible that multiple parties will have patents that, in effect, restrict the use of the same genes or proteins.

SUMMARY

Perhaps the disadvantages of the patent system (i.e., the "problem") can be summarized by the simple statement that too many parties have the possibility, at least, to obtain too many patents that affect the ability of scientists and others to do research, and the monopoly power obtained by the patentee is absolute.

POSSIBLE SOLUTIONS

What, then, can be the solutions? Possible solutions can be divided roughly into two categories—those that impact the number and nature of patents granted and those that affect the powers of the patentee once the patent has been obtained. Each of these approaches has at least two subtopics.

Pre-patent Considerations

With respect to restricting the number and nature of patents, it would be possible to change the nature of the subject matter that can be protected, and it would also be possible to alter the standards simply to make patenting more difficult.

According to the U.S. statute (35 U.S.C. § 101) subject matter that may be patented includes processes, articles of manufacture, machines, and compositions of matter. "Compositions of matter" has been held to include living organisms as long as they are not human and as long as they are artificially made, as decided by the Supreme Court in *Diamond v. Chakrabarty*.[11] *Chakrabarty* concerned genetically engineered microorganisms that had been modified so that they are able to gobble up oil spills. Since then, the U.S. Patent and Trademark Office Board of Appeals and Interferences has made decisions that clarify that animals and plants are also patentable.[12] A case before the U.S. Supreme Court[13] raises the question of whether utility patents are available for plants or whether this is a form of protection preempted by the Plant Variety Protection Act and the Plant Patent Act.[14] This has now been decided and plants do, indeed, qualify for utility patent protection.

Recent decisions of the Federal Circuit[15] have also clarified that algorithms, as long as they have a practical result, are patentable subject matter, as are business methods.[16] These decisions have merely interpreted the existing statutes as (1) not excluding from the definition of "process" a mathematical formula or business paradigm, again emphasizing that there must be a practical application included in the claim, and (2) not excluding from "machines" or "articles of manufacture" computer systems that carry out these processes.[17]

Actually, there is very little in the way of subject matter that is excluded from patentability, assuming that the standards of novelty, non-obviousness, and usefulness are met. The sole exception is that of human beings, which, one suspects, have been excluded as a matter of practicality. There is no statutory prohibition, and there is no court decision to this effect. The U.S. Patent and Trademark Office (U.S. PTO) has evidently decided that it is politically incorrect to issue such patents.

In view of this rather expansive interpretation of patentable subject matter, it is not surprising that products of nature, to the extent that they can be distinguished from their state as they occur in nature, have been long considered patentable. The earliest case on point acknowledged the patentability of vitamin B_{12} as the purified compound.[18] It was recognized that purified and isolated compounds such as vitamin B_{12} had an entirely different use from crude liver extracts. Of course, in this day and age, there are many existing patents on products of nature, including such useful pharmaceuticals as tissue plasminogen activator; nucleotide sequences encoding useful pharmaceuticals, such as tissue plasminogen activator, erythropoietin, human insulin, human growth hormone; and many others.[19] Many critics express surprise that, to use the language loosely, "genes" can be patented. The argument is that since the structure of the coding sequence, for example, for a useful protein, is already existent in nature and one need only "discover" it rather than "invent" it, this should not be patentable subject matter. But the Constitution makes no distinction between inventions and discoveries in discussing the patent system, and the statute itself addresses discoveries. Nevertheless, an intellectual distinction could be made. The question has been raised mostly in the context of discussion rather than in the context of actual application of the patent statutes by patent officers. Nucleic acids containing previously undisclosed nucleotide sequences are considered patentable subject matter by patent officers generally when claimed in a context other than that in which they are found in nature.

Although it is almost certainly too late to do it now, it would be theoretically possible to legislate a carve-out for products of nature. It might be difficult to define these, since in a sense everything is the product of nature until it is manipulated by human hands. Nucleotide sequences that are prepared in purified and isolated form, or prepared in contexts in which they normally do not exist, such as placed into expression vectors, have been manipulated by human hands. Is this different from a new chemical compound (which is acknowledged to be inventive) that just has naturally occurring atoms in contexts where they do not ordinarily exist? It might be possible to carve out a definition where the "natural product" retains its essential features in its new context and does not acquire any patentable new ones. Probably it is futile to discuss this possibility, since there is already so much precedent.

But it probably would not be beyond question to legislate out other kinds of subject matter, such as business methods. Again, there would be a definitional problem, but it would be easier to find support for this approach than for products of nature.

In contrast to the situation in the United States, excluding subject matter from patentability has a long tradition in many jurisdictions. Most jurisdictions exclude from patentable subject matter methods of treating human (and often,

animal) bodies or methods of diagnosis.[20] This is not as far-reaching as it sounds; for instance, claims can be obtained to the "use of compound *x* to treat disease *y*" or to the "use of compound *x* for the manufacture of a medicament to treat disease *y*" even in jurisdictions where methods of treatment are not patentable subject matter. (But these patents aren't the problem.)

The other exclusion that exists formally in other jurisdictions and only informally in the United States is one for subject matter that is contrary to the public order.[21] It is this exclusion that has undermined the effectiveness of the European patent on the Harvard oncomouse. Oppositions were filed, not by competitors or companies whose activities would be inhibited by this patent, but rather by organizations such as Greenpeace that oppose it on moral grounds. Opposition to patents on plants in the European Patent Office has also been mediated by such groups.[22]

In the context of the problem addressed here (the patent system inhibits research), it does not appear that excluding certain subject matter from the prospect of patentability is a very promising approach. The easy carve-outs don't address the problem; the carve-outs that would help are too difficult. The exclusion of compositions of matter that could become overlapping (such as partial gene sequences), in particular, is fraught with definitional and precedence problems.

With respect to the standards or criteria for patentability, however, attempts have been made to adapt the system to address the perceived problems. Subject-matter exclusions, in light of the statute as it exists and the interpretation of that statute by the courts, are the province of Congress. The standards for patentability, as long as they remain framed within the statutory/judicial context, are shaped in large part by the policies of the U.S. PTO itself. The U.S. PTO has considerable experience with this.

Of the three criteria for patentability (novelty, non-obviousness, and usefulness in the United States; novelty, inventive step, and industrial applicability elsewhere), only novelty is relatively free of interpretation. Either something is already in the public domain or it is not. "Non-obviousness" is said to be an "objective" standard but it is very far from that as a practical matter,[23] and "usefulness" has been equally problematic.

Perhaps the easiest way to frame this problem is to consider it as it applies to gene patenting as it has evolved in both the United States and Europe. There is an informative contrast in the essentially opposite, but symmetric, paths this evolution has taken. In brief, a proposed claim to a nucleotide sequence encoding a protein, for example, will easily meet the non-obviousness standard in the United States, but meet the usefulness standard only with difficulty; while in Europe such a claim would be considered prima facie non-inventive, but probably easily pass the standard of industrial applicability. In other words, in the United States your gene is not obvious but not very useful, and in Europe it's not inventive but industrially applicable.

In the United States, early decisions based on the classical paradigm of cloning a gene encoding a known protein placed great weight on the unpredictability of the resulting sequence and the necessity for defining and disclosing the sequence to define the composition of matter.[24] No one really foresaw, at the time these decisions were rendered, the full impact of the challenge posed by the new paradigm of rapid sequencing haphazardly. The early applications by the NIH for several thousand expressed sequence tag (EST) sequences[25] were stalled long enough to allow a change in the political climate to make them moot by virtue of their withdrawal. The essential holding of the early cases (*Amgen, et al.*) that the unpredictability of a retrieved sequence automatically made it non-obvious was never applied in those cases.

In addition, the U.S. PTO set an initial precedent that each individual sequence would not be considered a separate invention. The policy has now changed, and at this moment, the U.S. PTO is willing to consider only one nucleotide sequence per application. If that had been the policy at the time the NIH applications were filed, before the changes made by the accession of the United States to the General Agreement on Tariffs and Trade (GATT), it would have been quite advantageous to the applicant to consider each sequence separately. Prior to the GATT changes, the term of a U.S. patent extended 17 years from issue, i.e., the term was not measured from the date of filing. Thus, applicants could have pursued one or more sequences at their leisure, as their importance became known, reaching far into the future.[26] Upon the implementation of the GATT, which affects applications filed subsequent to June 7, 1995, the patent term runs 20 years from the date of filing. In this environment, that game could not be played. Any patent on any of the sequences contained in the original application would expire 20 years from the filing date regardless of when the patent issued. Therefore, unlike the pre-GATT situation, the applicant could not delay pursuing a patent on a sequence for, say, 15 years, and then expect to have the eventually issued patent expire 17 years after its issuance. The patent on that sequence would expire 20 years from the original filing date. The patent term in Europe traditionally ran from the date of filing, and so the European Patent Office could regard each sequence as a separate invention with impunity. There would be no way that the applicant could have prevented the patent on all of the sequences from expiring 20 years from the date of filing. This made the cost of pursuing multiple sequences in Europe prohibitive, since each sequence would require a separate application.

The European Patent Office (EPO) also takes the view

that once a protein is known, retrieving the gene encoding it is within the skill of the art, and the gene is inherently non-inventive unless there is some showing to the contrary. With regard to sequences obtained by random sequencing of a cDNA library or the genome, the EPO also regards this as lacking an inventive step. In this context, the distinction between the inventive step and obviousness requirements may be significant.[27]

Faced with decisions of the Federal Circuit that essentially guaranteed a finding of non-obviousness of a previously undisclosed sequence, the only criterion left for the PTO to employ in preventing the issuance of claims to thousands of sequences was the application of the utility (usefulness) requirement.[28]

Using "utility" to reject sequence claims seemed to work well. If a technician merely sequences random fragments from a cDNA library, it is pretty hard to tell what the sequenced nucleic acid would be good for. The approach most applicants have taken is to take a guess at the utility by homology to known sequences, or to assess what tissues the expressed sequence occurs in as some kind of a diagnostic. Such companies as Incyte, Celera, and HGS have compiled massive databases based on these philosophies. Nevertheless, the U.S. PTO has focused on the utility standard and issued guidelines designed to prevent patenting of sequences that have been disclosed only by aggressive sequencing. It has taken to heart the strictures of *Brenner v. Manson*[29] that a real-world utility must be proposed. For example, if the nucleotide sequence is considered to encode a receptor, function of this receptor must be known, and if the receptor is used as a screening tool, for example, it must be known what diseases could be treated by compounds found to interact with the receptor. If an antibody is claimed, it must be known what antigen the antibody interacts with and what use it would be to anyone to couple the antibody with the antigen. Oddly, nucleotide sequences that encode proteins that could be considered research tools, such as ligases or phosphatases, have automatic utility in that context. Why it is unquestioned what the research involving the ligase might be about, but questioned what the screening activity must be about, is unclear.[30]

In contrast, in the European Patent Office, since industrial applicability is the standard, this standard is almost automatically met. Clearly one could *sell* receptors as research tools for screening. The industrial applicability is right there.

Although many patents have issued on open reading frames encoding proteins, the imposition of these higher standards has been quite effective in preventing a multiplicity of patents on overlapping sequences. The U.S. PTO estimates that many more than half a million sequences are the subject of claims currently pending before the Office. We don't see half a million issued claims. Perhaps this bugaboo has already been taken care of.

It thus appears that at least some control over an undesirable number of overlapping patents has already been exerted by manipulating the standards for patentability as opposed to legislating changes in subject matter.

Post-patent Solutions

Turning now to the rights provided to the patentee, there are at least two possible approaches. One possibility is simply to exempt certain types of activity from infringement. There is considerable experience with this in the United States and elsewhere. The other possibility is to compel the patentee to license rights at reasonable rates under certain circumstances.

First, with respect to exclusions from liability, the best known example in the United States is the exemption under 35 U.S.C. § 271(e)(1). This provision excludes, as infringing acts, activities that are reasonably related solely to the securing of regulatory approval from the Food and Drug Administration (FDA). This exemption was inserted into the statute to reverse the holding in *Roche Prod. Inc. v. Bolar Pharm. Co.*[31] and was added at the same time provision was made for patent term extension based on delays in regulatory approval. The thought was that the holder of an approved New Drug Application (NDA) on a patented drug should not be allowed to prevent preparation of generic manufacturers to market the drug as soon as the patents expired. Therefore, the generic could submit an Abbreviated New Drug Application (ANDA) and conduct activities to secure approval without liability unless the ANDA applicant asserted that the patent was invalid or not infringed, in which case certain statutory provisions click in.[32] Assuming that there was no intention to market the drug until after the patent expired, the preclinical and clinical studies required to obtain approval would not be considered acts of infringement. As a counterweight, the ability of the patentee to retain a fair patent term, which might have been shortened by its own regulatory headaches, was provided by permitting the term of the patent to be extended in a fairly straightforward petitioning procedure.[33] Whether this statutory scheme is desirable has been the subject of some dispute, but it illustrates the fact that it is quite possible to legislate the exclusion of certain activities from liability. In the several cases that have tested the scope of this exemption, it appears that the courts have been fairly liberal in interpreting what activities are relevant to seeking FDA approval.[34]

A statutory exclusion that has received less attention lately is 35 U.S.C. § 287(c), which exempts medical personnel and institutions from infringement if they are merely carrying out a patented method of treatment that does not involve a patented or regulated drug or device. The provision was apparently passed in response to a vexatious suit

brought by the holder of a patent on a method for lens surgery, which eventually went away. There had been no real problem with doctors or hospitals being sued in the past, and the passage of the exemption from liability was probably an overreaction. A more appropriate response might have been similar to that of the Supreme Court in *Florida Prepaid Postsecondary Educ. Expense Bd. v. College Sav. Bank*,[35] which held that states were entitled to sovereign immunity from patent suits largely on the basis that states had not, for the most part, been abusing the patents of others.

Another proposed exemption from liability is a "research exemption," a concept that does exist as a judicially created doctrine.[36] However, the doctrine is quite narrow, and if there is any commercial purpose in the research, it generally does not fall within the exemption as the courts have molded it. Research for purely philosophical reasons, for example, to determine whether the invention works as disclosed, is certainly permitted,[37] but even a modest commercial purpose will take the practitioner outside the exemption.[38]

Both Europe and Japan have statutory exemptions for research, but again it becomes an issue of how "research" is interpreted, and the difficulties of definition appear to be quite large.

Alternatively, it would be possible to legislate a change from current law that the patentee's power to exclude is essentially absolute except for the eminent domain right of the U.S. government. Under GATT/TRIPS, compulsory licensing is permitted in certain defined circumstances,[39] and there is much to be said for applying such provisions to research tools. Perhaps this is the most direct way to counter the problem that a patentee can essentially prevent research from taking place by simply refusing to license or demanding too much in return for a license to research tools. The developer of the research tool would certainly be compensated for the contribution to science, but not at a prohibitive rate. Certain provisions in the GATT/TRIPS Agreement permit compulsory licensing where an attempt has been made to obtain a license but was unsuccessful, or where the patentee cannot supply sufficient quantities of a patented medicament, for example (see endnote 39).

Compulsory licensing for non-working is actually in effect in a number of jurisdictions, including many European countries and Japan.[40] "Non-working" refers to a situation where the patentee is not practicing the invention in the jurisdiction in question. Thus, for example, if the patent is directed to a drug and the drug is not made available in the jurisdiction in which the patent is held, the patentee may be forced to license someone else to provide the drug in that jurisdiction. It is unclear to what extent these provisions have had to be resorted to, since their presence probably encourages voluntary licensing under reasonable terms upon request.

CONCLUSION

There does appear to be a disconnect between the current structure of the patent system and the research efforts made both by private and public institutions. Largely, this may result from abuse of the monopoly provided on research tools as opposed to commercial products. The solution to this problem may lie in stanching the flow of arguably undeserved patents (as in the case of non-annotated gene sequences) and by compelling patentees with claims to research tools to license their inventions at reasonable rates.

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ENDNOTES

[1]The U.S. government does, of course, expend billions of dollars to finance research sponsored by the National Institutes of Health, the Department of Defense, the Department of Energy, and other agencies. The inventions and discoveries made by government employees, as well as those made by recipients of government grants, are essentially fully integrated into the patent system. The Bayh–Dole Act, passed in 1980, which provided a uniform system for dealing with inventions made with government funds, was intended to encourage the exploitation of government-funded inventions. A detailed economic study of the integration of government projects with the capitalist system of private profit is beyond the scope of this paper.

[2]Can hospitals as a group still be considered non-commercial institutions? The majority of teaching hospitals affiliated with medical schools, in which research and innovation occur, are nonprofit, but hospitals in general appear to be moving toward commercialization.

[3]Basic and unfocused research is sometimes the most productive. Examples include the discovery of restriction enzymes in the context of studying the manner in which prokaryotes defend against phage infection and the invention of the polymerase chain reaction (PCR).

[4]Most jurisdictions have been publishing patent applications 18 months from their priority dates for years. In the American Inventors Protection Act of 1999, publication of U.S. applications prior to issue was authorized for the first time for applications filed after November 29, 2000. Such an application is published 18 months from its earliest priority date unless there is certification that the application will not be filed elsewhere. (The exception for applications filed only in the United States is designed to accommodate the interests of the "independent inventor" who fears that disclosure of an invention prior to issuance of the patent will lead to theft of the idea.) If the certification is made and the applicant changes his or her mind, the U.S. PTO must be notified within 45 days or the U.S. application is abandoned.

[5]Most jurisdictions operate on an absolute-novelty basis; i.e., patent protection cannot be obtained if the claimed invention is anticipated or made obvious by public disclosure anywhere in the world prior to the application. The United States has a one-year statutory bar—i.e., patentability is not precluded per se if the application is filed within one year of publication. This statutory bar applies to publications by either the inventor or others since the United States still operates on a first-to-invent system. Canada has a one-year grace period; patentability would be defeated by a publication by another within the prior year, but publication by the inventor himself or herself does not bar patentability in Canada. Japan has a six-month grace period that operates on a rather complicated scheme.

[6]This does sometimes still happen, but it is not supposed to. A researcher who is paid by a corporate body, including a university, is supposed to send the material only on condition that a Material Transfer Agreement is executed.

[7]Government fees in the United States are relatively modest, $750 for filing and $1,200 for issue (half that for nonprofits or small entities), but foreign filing costs are tremendous. We estimate the cost to file a European application is on the order of $10,000, and the cost to file an application in Japan is about the same. (This does include service fees for associated agents in other countries.) And that is only the beginning. There will be grant fees and annuities to be paid. To obtain national patents in all 18 members of the European Patent Office (EPO), for example, the cost is of the order of $50,000. Each country will then charge its own annuities.

[8]Fortunately, only a small percentage of U.S. patent applications wind up in interferences (about 0.1%), but the percentage goes up in hot areas such as biotechnology. Depending on how one classifies the applications, the percentage in these areas is 2–4%.

[9]For instance, Housey Pharmaceuticals has requested large sums from licensees to use its patented assay. A recent case involving these patents has been partially decided; however, summary judgment against Housey regarding a claim of patent misuse was denied as involving factual inquiries. *Bayer v. Housey Pharmaceuticals*, Civil Action 01-148SLR (DC Del, Oct 17 2001). This is an interesting case: the proposed license which imposed royalties on compounds discovered by the patented assay would obligate the licensee to pay these royalties even after Housey's patents expired. It is this aspect that was considered supportive of patent misuse. A finding of "patent misuse" will preclude enforcement of the patent unless the misuse is corrected.

[10]*See* 28 U.S.C.A. § 1498 (West Supp. 2001); *and* Exec. Order No. 10,789, 3 C.F.R. 426 (1954–1958 Comp.).

[11]447 U.S. 303, 206 USPQ 1993 (1980).

[12] See *Ex parte Allen*, 2 USPQ2d 1425 (Bd. Pat. Apps. & Int. 1987); *Ex parte Hibberd*, 227 USPQ 443 (Bd. Pat. Apps. & Int. 1985).

[13]*J.E.M. AG Supply Inc. v. Pioneer Hi-Bred Int'l Inc.*, 200 F3d 1374, 53 USPQ2d 1440 (Fed. Cir. 2000), *cert. granted*, U.S. No. 99-1996 (Oral Arguments Oct. 3, 2001).

[14]The Plant Variety Protection Act is essentially a protection for seeds and contains limits on exclusivity, such as farmers' exemptions. The Plant Patent Act applies to asexually propagated plants and is limited to plants physically derived from the patented species. Both kinds of protections are quite different from standard utility patents, a number of which have been issued on genetically engineered plants. The decision is reported at *Pioneer Hi-Bred v. JEM Supply*, 122 JCt 593, 152 LEd 2d 508 (2001).

[15]The Court of Appeals for the Federal Circuit was created in 1980 and serves, among other functions, as the exclusive appeals court for patent cases. Since patents are governed by Federal statutes, patent infringement cases are tried in District Courts. Appeals from patent cases, rather than going to the various circuit courts of appeals, go instead to the Federal Circuit. Appeals from decisions made by the Patent Office itself may also be made to this court (in addition to an alternative civil procedure before the District Court of the District of Columbia). The Court of Appeals for the Federal Circuit generally hears cases before three-judge panels, but occasionally a case is considered of sufficient importance to be heard *en banc*.

[16]*State Street Bank & Trust Company v. Signature Financial Group, Inc.*, 149 F3d 1368, 47 USPQ2d 1596 (Fed. Cir. 1998); *A.T.&T. Corp. v. Excel Communications, Inc.*, 172 F3d 1352, 50 USPQ2d 1447 (Fed. Cir. 1999).

[17]The flurry of activity of obtaining patents on business methods has led to a good deal of both litigation and criticism. Business methods in particular have been suspect because the experience of the business community in carrying out its activities is not well documented publicly. This results in there being a lack of prior art accessible to the Patent Office in examining applications in these areas.

[18]*Merck & Co., Inc. v. Olin Mathieson Chemical Corp.*, 253 F2d 156, 116 USPQ 484 (4th Cir. 1958).

[19]It had been relatively difficult to obtain patents on purified and isolated actual proteins since many of those known to be useful had already been purified and isolated in the prior art.

[20]*See e.g.*, Japanese Patent Law, Law No. 121 of 1959, art. 29, no. 2-1.

[21]*See* European patent law exceptions to patentability EPC Art. 53 (a) and (b):

> inventions the publication of which would be contrary to "ordre public" or morality, and plant or animal varieties or essentially biological processes for the production of plants or animals; this provision does not apply to microbiological processes or the products thereof.

Japanese Patent Law, Law No. 121 of 1959, Art. 32:

> The following inventions shall not be patented, notwithstanding Section 29;
>
> (i) inventions of substances manufactured by the transformation of the atom (not anymore valid)
>
> (ii) inventions liable to contravene public order, morality or public health.

[22]*Plant Genetic Systems*, Case T 356/93 [1995] OJ EPO 545.

[23]The 1952 patent statute officially did away with any "flash of genius" requirement. Prior to the passage of the statute, there were a number of decisions that implied that in order to be patentable some particular mental state of the inventor had to be obtained, for example by a sudden inspiration or "flash of genius." The statute provides for what is supposed to be an "objective" standard—i.e., whether one of ordinary skill in the art would have found the invention obvious. This statute explicitly states that "patentability shall not be negatived by the manner in which the invention was made". There are a number of factual issues to be decided in evaluating obviousness, (*Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966)); but in the end, it is a straight judgment call.

[24]*In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995); *In re Bell*, 999 F2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993); *Fiers v. Sugano*, 984 F2d 1164, 25 USPQ2d 1601 (Fed. Cir. 1993); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016 (Fed. Cir. 1991) *cert. denied*, 502 U.S. 856 (1991).

[25]An EST (expressed sequence tag) is a DNA sequence encoding a short segment of a cDNA clone that is chosen from a set of cDNA clones obtained by known procedures.

[26]These circumstances (if a hypothetical applicant were to file multiple continuing or divisional applications over a time period covering particular sequences contained in an original application) would typically give rise to concerns of potential "obviousness-type" double-patenting rejections arising during prosecution of later filed applications. One method of dealing with these types of rejections would be through the use of "terminal disclaimers" under 35 U.S.C. 253, i.e., if common ownership requirements are met, an applicant would specify that later-issued, and purportedly related, patents will expire at the same time as earlier-filed applications that have issued. Under this regime, if a patent issued, for example, on a first sequence, and a second sequence were considered just an obvious variation, a later issued patent on the second sequence would expire at the same time as that issued on the first. Had the Patent Office required on its own that separate applications be filed for each sequence, however, it would have been prevented from demanding these terminal disclaimers. Therefore, the applicant could stagger obtaining patents on multiple sequences so that the later issued patents would expire at a time determined by their own issue dates, long after the first patents in the series.

[27]This distinction can readily be seen in the words themselves. "Obviousness" appears to focus on the nature of the answer or result; inventiveness appears to focus on the process used in obtaining that result.

[28]This is not quite true: citing cost factors, the PTO arbitrarily decided at

first that only ten unrelated sequences could be combined in an application, and then limited examination to only one sequence per application. The utility requirement appeared to be the first real line of defense.

[29]383 U.S. 519, 148 USPQ 689 (1966)

> [A] process patent in the chemical field, which has not been developed and pointed to the degree of specific utility, creates a monopoly of knowledge which should be granted only if clearly commanded by statute. Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development, without compensating benefit to the public. The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> . . . We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product. That proposition seems to us little more than an attempt to evade the impact of the rules which concededly govern patentability of the product itself.

Ibid. at 534-35.

[30]The Guidelines require that utility for a composition of matter or a process must be credible, substantial, and specific. The term "credible" means that one of ordinary skill would not doubt the truth of the utility once it is asserted. This has caused considerable problems with regard to potential uses of materials related to medical technology, as the inherent unpredictability of therapies and preventive medicine is often cited. The decision in *In re Brana*, 34 USPQ2d 1437 (Fed. Cir. 1995), has made clear that the Patent Office is not the Food and Drug Administration, and that clinical results are not required to support a nexus between patented subject matter and pharmaceutical utility. Nevertheless, the question of the unreliability of animal models, asserted irrelevance of *in vitro* assays, and the like often arises.

The term "substantial" means that the use must be something other than trivial. The classic example is claiming a chemical compound for use as a paper weight when placed in a jar. The PTO's current example is the use of transgenic mice as snake food. Sometimes it is difficult to distinguish "substantial" from "specific." But, by "specific" the Patent Office appears to mean that the use for a claimed nucleic acid must be specific to the nucleotide sequence contained therein, and not true of nucleic acids in general. For example, it is insufficient simply to designate an oligonucleotide as a "probe" unless it is clear what it is that is being probed for and why anyone wants to probe for it.

[31]733 F2d 858, 221 USPQ 937 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 856 (1984).

[32]35 U.S.C. § 355(j)(2)(A)(vii)(IV) (paragraph IV certification). Filing for this certification requests that the FDA approve the ANDA application and permit commercialization prior to expiration of the listed patent. Here the applicant must present factual and legal arguments why the disputed patent either is not infringed or is invalid, and the patentee has 45 days to bring suit for infringement, so that these arguments can be tested in court.

[33]35 U.S.C. § 156.

[34]*Eli Lilly and Co. v. Medtronic, Inc.*, 496 U.S. 661, 15 USPQ2d 1121, *rehearing denied*, 497 U.S. 1047 (1990); *AbTox Inc. Exitron Corp.*, 122 F3d 1019, 43 USPQ2d 1545 (Fed. Cir. 1997); *Bristol-Myers Squibb Co. v. Royce Lab.*, 69 F.3d 1130, 36 USPQ2d 1641 (Fed. Cir. 1995); *Intermedics v. Ventritex Co.*, 991 F.2d 808, 26 USPQ2d 1524 (Fed. Cir. 1993); *Baxter Diagnostics Inc. v. AVL Scientific Corp.*, 798 F.Supp. 612, 25 USPQ2d 1428 (C.D. Cal. 1992); *Intermedics, Inc. v. Ventritex, Inc.* 775 F.Supp. 1269, 20 USPQ2d 1422, *affirmed*, 991 F.2d 808, 26 USPQ2d 1524 (Fed. Cir. 1991).

[35]527 U.S. 627, 51 USPQ2d 1081 (Sup. Ct. 1999) ("The examples of States avoiding liability for patent infringement by pleading sovereign immunity in a federal-court patent action are scare enough, but any plausible argument that such action on the part of the State deprived patentees of property and left them without a remedy . . . is scarcer still." *Ibid.* at 647, 51 USPQ2d at 1090).

[36]*See Whittemore v. Cutter*, 1 Gall. 429, 29 F.Cas. 1120 (C.C.D. Mass. 1813).

[37]*See ibid.* at 1121 ("[I]t could never have been the intention of the legislature to punish a man, who constructed such a machine merely for philosophical experiments, or for the purpose of ascertaining the sufficiency of the machine to produce its described effects.").

[38]*Spray Refrigeration Co. v. Sea Spray Fishing*, 322 F2d 34, 138 USPQ 470 (9th Cir. 1963), *Infigen, Inc. v. Advanced Cell Technology, Inc.*, 65 F. Supp. 2d 967 (WD Wis. 1999); and *Baxter Diagnostics, Inc. v. AVL Scientific Corp.*, 924 F.Supp. 994 (CD Calif. 1996).

[39]These circumstances are provided under Article 31:

> Where the law of a Member allows for other use of the subject matter of a patent without the authorization of the right holder, including use by the government or third parties authorized by the government, the following provisions shall be respected:
>
> (a) authorization of such use shall be considered on its individual merits;
>
> (b) such use may only be permitted if, prior to such use, the proposed user has made efforts to obtain authorization from the right holder on reasonable commercial terms and conditions and that such efforts have not been successful within a reasonable period of time. This requirement may be waived by a Member in the case of a national emergency or other circumstances of extreme urgency or in cases of public non-commercial use. In situations of national emergency or other circumstances of extreme urgency, the right holder shall, nevertheless, be notified as soon as reasonably practicable. In the case of public non-commercial use, where the government or contractor, without making a patent search, knows or has demonstrable grounds to know that a valid patent is or will be used by or for the government, the right holder shall be informed promptly;
>
> (c) the scope and duration of such use shall be limited to the purpose for which it was authorized, and in the case of semi-conductor technology shall only be for public non-commercial use or to remedy a practice determined after judicial or administrative process to be anti-competitive;
>
> (d) such use shall be non-exclusive;
>
> (e) such use shall be non-assignable, except with that part of the enterprise or goodwill which enjoys such use;
>
> (f) any such use shall be authorized predominantly for the supply of the domestic market of the Member authorizing such use;
>
> (g) authorization for such use shall be liable, subject to adequate protection of the legitimate interests of the persons so authorized, to be terminated if and when the circumstances which led to it cease to exist and are unlikely to recur. The competent authority shall have the authority to review, upon motivated request, the continued existence of these circumstances;
>
> (h) the right holder shall be paid adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization;
>
> (i) the legal validity of any decision relating to the authorization of

such use shall be subject to judicial review or other independent review by a distinct higher authority in that Member;

(j) any decision relating to the remuneration provided in respect of such use shall be subject to judicial review or other independent review by a distinct higher authority in that Member;

(k) Members are not obliged to apply the conditions set forth in subparagraphs (b) and (f) where such use is permitted to remedy a practice determined after judicial or administrative process to be anti-competitive. The need to correct anti-competitive practices may be taken into account in determining the amount of remuneration in such cases. Competent authorities shall have the authority to refuse termination of authorization if and when the conditions which led to such authorization are likely to recur;

(l) where such use is authorized to permit the exploitation of a patent ("the second patent") which cannot be exploited without infringing another patent ("the first patent"), the following additional conditions shall apply:

(i) the invention claimed in the second patent shall involve an important technical advance of considerable economic significance in relation to the invention claimed in the first patent;

(ii) the owner of the first patent shall be entitled to a cross-licence on reasonable terms to use the invention claimed in the second patent; and

(iii) the use authorized in respect of the first patent shall be non-assignable except with the assignment of the second patent.

[40] *See e.g.*, Japanese Patent Law, No. 121 of April 13, 1959, art. 83; *and* Patents Act 1949, Section 37 (c. 87) (Eng.). It is my understanding, however, that this is rarely, if ever, used.