PATENTABILITY OF BIOTECHNOLOGY INVENTIONS UNDER THE PTO UTILITY GUIDELINES: STILL UNCERTAIN AFTER ALL THESE YEARS?

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ABSTRACT

The U.S. Patent and Trademark Office ("PTO") recently published its final version of guidelines to be used by its patent examining corps in determining the patentable utility of an invention (the "Guidelines"). This Article discusses some implications of the Guidelines. The utility requirement of U.S. patent law serves to increase the likelihood that a patent will issue whose scope is well-defined and serves to increase the certainty that prior knowledge can correctly predict the utility of a new invention. The desire to manage unpredictability forms the basis of the tripartite utility test which introduces the idea of a 'credible' use to the already-established 'specific' and 'substantial' use tests. The Guidelines introduce some procedural and substantive uncertainty that will need to be sorted out over time.Specific biotechnology issues in this regard relate to the patentable utility of ESTs, SNPs, research tools and the concept of utility based on DNA/protein database homologies. The utility Guidelines also highlight the larger context of access to biotechnology patents. Several biotechnology-related business and legal decisions are discussed that arise from the Guidelines. The Guidelines are a step in the right direction but uncertainties remain, given the nature of much of the technology that interacts with them.

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INTRODUCTION

On January 8, 2001, the U.S. Patent and Trademark Office ("PTO") published guidelines to be used by its patent examining corps in determining the patentable utility of an invention (the "Guidelines").[1] Although the Guidelines are intended to be technology-neutral, they are the culmination of efforts begun in the mid 1990's on the part of the PTO and industry, academia, and private citizens to resolve lingering questions about the issue of 'utility' and patentability of recombinant DNA methods and compositions. The Guidelines do not have the force of law. Nonetheless, in conjunction with published comments to the Guidelines[2] and supported by PTO legal analyses and certain training materials still under PTO review[3], they are intended to provide attorneys, scientists and business people with some certainty as to the meaning of "utility" under U.S. patent law[4]. The implications of the Guidelines go well beyond their literal language and they illuminate, but cannot yet fully resolve, the issues created in this context. In addition to addressing the criteria for utility with regard to patenting DNA and proteins, the published questions and responses in the Guidelines respond to broader social and legal concerns about patenting 'life'.

The backdrop to this debate is the U.S. Supreme Court's view of the utility requirement in Brenner v. Manson[5] and its present form as interpreted by the PTO and shaped by the courts. The Court's reasoning in Brenner v. Manson, before the advent of biotechnology, still informs the present discussion and has particular significance for questions regarding the utility of research tools and the ability to show patentable utility for DNA and protein based upon previously known and structurally similar ("homologous") nucleotide and amino acid sequences.[6] These issues reveal themselves very clearly in the legal and extra-legal discussions leading up to publication of the Guidelines.

This article is divided into five sections. Section 1 is a background - briefly summarizing the history of the utility requirement in U.S. patent law and its modifications and provides the legal background behind the Guidelines. It introduces the concept that the 'utility' requirement, as interpreted by the Supreme Court, is intended to reduce uncertainty present in the granting of a patent. That is, the utility requirement in U.S. law serves to increase the likelihood that a patent will issue whose scope is well-defined and serves to increase the certainty that prior knowledge can correctly predict the utility of a new invention. Section 2 is a summary of the key aspects of the Guidelines and how the desire to manage unpredictability forms the basis of the tripartite utility test. Section 3 examines some issues specific to biotechnology such as the patentable utility of ESTs, SNPs, research tools and utility based on homologies. Section 4 broadens the discussion to introduce the concept of managing unpredictability in the context of access to biotechnology patents and places the issues in larger perspective by analyzing some issues about 'gene patents'. Section 5 briefly reviews proposed modifications to the 'utility' requirement that are in response to the broader societal issues raised by the patenting of, and access to, gene sequences.

BACKGROUND

In 1991, the National Institutes of Health (NIH), under the direction of Harold Varmus, fild for patents on uncharacterized gene fragments (i.e., Expressed Sequence Tags, or ESTs) that were sequenced using federal sponsorship. Ostensibly, the NIH patent application was filed to establish government rights over the sequences before private compnanies applied for patents on the same sequences. Initially, the PTO rejected the patent application, in effect forcing the decision on patentability of ESTs onto the patent appeals process and possibly to the federal courts. The NIH withdrew its application before any third party had a chance to rule.

This episode brought the controversy over patent uncharacterized gene fragments or sequences with no clear and specific utility to the national agenda. It led to PTO to consider clearer guidelines on the "utility" criteria for awarding patents on non-coding genes or genes whose protein products had not been characterized.

The utility standard is found in Section 101 of title 35, United States code which reads: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title"[7]. The statute serves two purposes: it defines which categories of invention are eligible for patent protection and it ensures that patents are granted only on those inventions that are 'useful'. This second purpose is grounded in Article I, Section 8 of the Constitution which authorizes Congress to provide exclusive rights to inventors to promote the 'useful arts".[8]

The utility requirement standards have shifted over time. In Lowell v. Lewis[9], Justice Story explained the utility requirement as having a low bar, i.e., the law requires that an invention "... should not be frivolous or injurious to the well-being, good policy or sound morals of society. The word 'useful' therefore, is incorporated ... in contradistinction to mischievous or immoral".[10] Indeed, for many years prior to the Supreme Courts' decision in Brenner v. Manson,[11] the Patent Office granted, with courts' approval, patents to chemical compositions without any inquiry into their utility.[12]

That substantially changed with the Manson patent applications. In re Manson[13] claims in Manson's patent application directed to a method of making a steroid were rejected by the Patent

Office over an already issued patent.[14] The steroids so made had no known use at the time and the Patent Office, in rejecting the method claims, asserted that Manson's application required a statement of utility for the compounds made by the method. Manson made the following allegations in reply: a) his process was capable of making a product which satisfied the requirements of Section 101; b) a known homologue to the product actually had utility and c) the claimed process produced a product that was being actively screened by scientists for possible use.[15] He appealed the Patent Office decision and also filed papers requesting that an interference be declared between his patent application and the issued patent.[16] The patent appeals tribunal demurred to Manson's request, saying that the products made by his claimed process had no utility, thus precluding him from obtaining allowed claims and from provoking the interference.

The Court of Claims and Patent Appeals ("C.C.P.A"; the predecessor of the Court of Appeals for the Federal Circuit) reversed, asserting that Manson needed to show nothing more than that the process operated as claimed and that it produced a compound (whether 'useful' or not) as intended by his description.[17] In Brenner v. Manson, the Supreme Court reversed the C.C.P.A[18] and, in response to Manson's three allegations (above) held that: a) a process patent needs to show that the product so produced has a 'practical utility' in order to satisfy Section 101; b) there was no evidence that Manson's data showed a 'sufficient likelihood" that the steroid made would have similar properties to the known homologue; c) a product has no patentable utility if its only use is as an object of further scientific research.[19] The policy implications of this holding are with us more than thirty years later.

The Court developed several reasons for denying Manson's request to initiate the interference. The most well thought-out consideration was based on the fact that a patent grant is an exclusionary right, such that patent owner can prevent others from, among other acts, making, using or selling that which is described in a particular claim of an issued patent.[20] The key passage in Brenner v. Manson that implicity foreshadows many of the issues raised by the patenting of DNA and protein is the following:

" ... [u]ntil the process claim has been reduced to production of a product shown to be useful, the metes and bounds of the monopoly are not capable of precise definition. 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 application to engross what may prove to be a broad field".[21]

The Court appeared to be saying that until the inventors' work was sufficiently advanced in practical use such that the public could have some certainty as to the boundaries of what was to be excluded, the work was not to be afforded the right to be exclusive. Brenner v. Manson created quite a bit of controversy among practitioners and legal scholars.[22] In particular, note that the 'metes and bounds' of a product or process claim in a patent are not actually limited by the uses described in the patent, unless a use is expressly written into the claim itself.[23] Subsequent Federal courts have interpreted the Brenner v. Manson utility requirement to mean that patent applicants identify a 'specific and substantial' (i.e., a practical, 'real world') utility for the invention for which patent protection is sought.[24] Clearly, Brenner v. Manson left unresolved the question of what actually is required in the way of reducing the risk that the patent granting process will lead to a patent with undefinable 'metes and bounds'. The courts and the PTO have struggled with this every time new technology and innovation become subject to the patent system.

Two cases inform discussions about utility for biotechnology inventions and serve to summarize evolution of this concept in the time period preceding the Guidelines. In Cross v. Iizuka,[25] the Federal Circuit was called on determine the degree of proof needed to show pharmacological activity of a series of thromboxane synthetase inhibitors, considered to be useful in treating inflammation, asthma and

hypertension.[26] The court noted that adequate proof of pharmacological activity (which is clearly a practical utility under Brenner v. Manson) will satisfy the Brenner v. Manson standard and that structural similarity to known pharmacologically active compounds can establish utility.[27] This panel grappled with the issue of the whether the utility shown in the prior art was sufficiently predictive of the claimed invention such that a patent should be awarded to certain compounds. In the words of Brenner v. Manson, the "metes and bounds" of the resulting patent needed to be capable of definition.

In In re Brana,[28] the Federal Circuit addressed the question of what sort of experimental test systems were specific enough for an asserted human therapeutic utility and the question of whether the asserted therapeutic utility was credible based on these tests. Brana disclosed a series of organic compounds for use as anti-tumor substances. Brana employed both in vitro experiments and an in vivo mouse model to test the anti-tumor activity of his compounds and compared the claimed compounds to structurally similar ones known to have similar properties.[29] Brana's materials were superior in these tests. The court found the test systems appropriate and sufficient to support the specific therapeutic utility asserted for the compounds.[30]

Two assertions prefigure some of the issues discussed in the Guidelines. In the first, the Brana court held that in vitro tests were adequate to convince a person having ordinary skill in the art (hereinafter "PHOSITA") that the compounds were useful since, among other things, " ... the prior art discloses structurally similar compounds to those claimed by the applicant which have been proven in vivo to be effective....".[31] Again, the court based its position on the fact that the claimed compounds were useful precisely because their activity was predictable from similar, clearly 'useful' compounds. This echoes the Brenner v. Manson concept of reducing uncertainty regarding what is being excluded in the patent grant. Further, the Brana court held that in vivo tests did not have to show clinical results in humans and that tests with standard experimental animals would be sufficient. In this regard, the court stated that " ...FDA approval is not a prerequisite for finding a compound useful within the meaning of the patent laws."[32] The court further said, " ... [u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development".[33] At least one commentator has taken the position that this sentence acknowledges indirectly that Brenner v. Manson was incorrectly decided and that chemical intermediates and research tools (both of which arguably are used only as an 'object of further scientific research), should really be patentable under Section 101.[34]

The complaints against the Patent Office's handling of the utility requirements with regard to testing for human therapeutic uses prior to Brana had brought the utility requirement to wider attention. Moreover, the filing of patent applications, including those of the NIH, containing expressed sequence tag sequences (ESTs) and obtained by massive but routine methods, raised the fear in the biomedical community that such sequences (having no apparent biological function) would issue and confound later innovations on the actual biological use or on method claims in which the biological function was actually identified. This refrain clearly mirrors the Brenner v. Manson consideration.

In 1994, the PTO held a meeting in San Diego in which they were castigated by the biotechnology industry on these matters.[35] Following this meeting, the PTO opened up the question of utility for public discussion, leading to their promulgation of the 1995 utility guidelines.[36] The PTO also had received comments on patentability of ESTs in the context of comments to guidelines directed to the "written description requirement" of the patent code.37 The Patent Office incorporated some of the EST comments into its revised utility guidelines.[38] On Jan. 8, 2001, the PTO published its final Utility Examination Guidelines.[39]

THE GUIDELINES

A. PROCEDURAL ISSUES

The analysis for deciding patentable utility as set forth in the Guidelines is a framework for allowing the Patent Office to determine the predictive value of the prior art, the value of disclosure and the knowledge at the time the patent application was filed, in predicting whether a claimed invention has

Section 101 'utility'.[40]

When claims are rejected based on the Guideline analysis, the burden of coming forward with evidence is shifted to the inventor who must provide evidence that there is a specific and substantial utility and that a PHOSITA would know this specific and substantial utility was established at the time of filing.[41] Further sections define what the Patent Office has to show when it rejects a claim for lack of utility. It must provide documentary evidence and explanations for rejections based on no 'specific and substantial credible' utility.[42] The Guidelines further provide some safeguards against overzealous patent examiners. The PTO must take as true any factual statements related to an asserted utility unless there is evidence that a PHOSITA would doubt the credibility of the statement. Expert testimony is not to be disregarded just because PTO disagrees, unless its accuracy is questioned.[43]

B. SUBSTANTIVE ISSUES

ADDING "CREDIBILITY": THE 3 PART TEST

The PTO has introduced the concept of 'credibility' into the former two prong Brenner v. Manson test.[44] The PTO has stated that an asserted utility is credible unless the logic underlying the assertion is flawed or the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.[45] In the doctrinal sense, addition of a new member to the "specific and substantial" dyad is not a major step since requiring a "credible" use was at least implied in In re Brana.[46] In theory, adding another test introduces extra information into the utility analysis and may provide more certainty going forward, leading to reduced risk of patenting a 'useless' invention, i.e., one whose 'metes and bounds' (in the words of Brenner v. Manson) are not clearly delineated. Addition of a requirement that the inventor show a 'credible' utility at the time of filing anchors the three-part test in a consideration of whether a PHOSITA would accept that the invention is available for such use. In practical terms, it may well be that the 'credibility' of uses for DNA, SNPs as probes or diagnostic markers will almost always be supportable since the level of "ordinary" skill of this hypothetical PHOSITA is going to be quite high. As a result, the three-part test may, in many cases, collapse back into the Brenner v. Manson, 'specific and substantial' test. What effect this has on patenting biotechnology inventions remains to be seen.

ASYMMETRIES AND DOCTRINAL CONFUSION

The Guidelines suggest that the PTO will give claims to a DNA composition based on homology to known DNA compositions, if the discovered DNA asserts a specific, credible, and substantial utility that is predictable from its structural relationship to an existing family of DNA. This existing DNA also must display specific, credible and substantial (i.e, patentable) utility. [47] We note that the Supreme Court had only required Manson to show a "substantial likelihood" that his steroids had similar properties to known homologues.[48] The language in the Guidelines extends this to now suggest that an existing family of compounds must have a use sufficient, in effect, to allow such existing compounds to pass the tripartite "utility" bar. This appears consistent with the notion emanating from Brenner v. Manson that quantifying uncertainty lies at the heart of the utility requirement In theory, this is probably the correct way of ensuring a level of certainty/predictability in existing materials sufficient to create a legally supportable benchmark from which to evaluate the uses of an unknown, claimed compound.

In many cases, however, the prior knowledge about the uses of an existing family of compounds or molecules may not be sufficient to rise to the level of patentability required by the Guidelines. Thus, at one extreme, prior knowledge could be a U.S. patent which is presumed useful.[49] Prior knowledge may also consist of an abstract, poster session or electronic publication falling short of the 'specific, substantial and credible' criteria. Moreover, an existing group of compounds may not be in the public domain at all. In that case, will it be available to be used as a 'utility' benchmark if there has been no public knowledge or use?[50] How this will play out in the Patent Office and in the courts may be important to determining utility

based on homology.

Moreover, this suggestion that an existing group of compounds must have patentable utility exaggerates existing asymmetries in patent law. Thus, a previously described compound can render a claimed compound unpatentable because of lack of novelty, even though the prior compound has no utility at all.[51] Prior art does not have to be operable to render a claimed invention 'obvious'.[52] In an interference, in order to show priority of invention, the inventor must prove a reasonable utility based on the problem to be solved but there appears to be no explicit requirement of 'specific and substantial' utility.[53]

Perhaps even more significantly, the Federal Circuit has already introduced some uncertainty of their own by putting a gloss on the U.S. Patent Office's utility standard. In State Street Bank and Trust Co. v Signature Financial Group, Inc.,[54] a very important non-biotechnology case that altered the law of patenting so-called "business methods", the Federal Circuit stated that the patent at issue (which claimed a method whereby mutual funds can pool their assets in an investment portfolio organized as a partnership) produced a 'useful, concrete, and tangible result...".[55] Perhaps the court really meant 'specific, substantial and credible..." since the State Street case was decided well after the first Patent Office guidelines were promulgated. One can hardly overstate the doctrinal confusion if there really is a separate Patent Office utility requirement and another, Federal Circuit-created requirement for business methods.[56]

UNPREDICTABILITY, PATENTING ESTS, SNPS, RESEARCH TOOLS, HOMOLOGUES

A. Research Tools

For reasons outlined above, the concept of eliminating unpredictability is central to the Brenner v. Manson holding that one cannot patent materials lacking specific and substantial "real world" utility. It follows then that one should not be able to patent inventions whose use is: a) not predictable from prior art; and/or b) not predictable from assertions or data that are known at the time of filing; and/or c) not predictable from assertions found in the patent application. The Patent Office's tripartite test is designed to assay the quantum of predictability. The critical part of the tripartite test that implicates this predictive value is the 'substantial' prong of the test. The training materials are worth quoting at length:

" ... Utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a 'substantial utility' define a 'real world' context of use. An assay to measure the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a 'real world' context of use in identifying potential candidates for preventative measures or further monitoring".[57]

The training materials provide examples of patent claims that define an invention lacking 'substantial' utility, i.e. the claim scope would be unpredictable in the sense of requiring further research to identify or confirm a 'real world' use. The following inventions (some of which might be used as research tools) will not pass the utility test: an assay to measure some material having no specific and substantial utility, a protein in which further research is needed to figure out a specific and substantial utility; assay methods for identifying products which have no specific and substantial use, a method of making something that has no specific and substantial utility, transgenic animals containing specific DNA sequences but no indication that the absence or presence of a specific protein encoded by the DNA is associated with a disease. Frankly, these are likely to be the easy, trivial examples. The Patent Office will almost certainly be dealing with fact patterns much more subtle and complex than these.

Although the results of research may not be known at the time of filing a patent application, it is good public policy not to deny the benefits of the patent system to society, if by further development of a research tool, a PHOSITA can use the claimed compound or method to realize a credible, practical application. At present, the developer of a research tool may not gain these benefits until they

develop a 'real world' use for it. The utility of research tools will continue to be the subject of future negotiations between the stakeholders, i.e., the Patent Office, the scientific community, and the courts.

B. Expressed Sequence Tags (ESTs)[58]

The Guidelines also seem to suggest that genes are theoretically patentable even with a partial sequence inasmuch as the utility of a claimed DNA does not "necessarily depend on the function of the encoded gene product".[59] This statement is important since the Patent Office is clearly saying that ESTs do not inherently lack statutory utility. The Guidelines suggest that a claimed partial DNA may have 'real world' utility as a marker for another disease-associated gene or as a regulator of another gene.[60] Nonetheless, the training materials (which almost certainly will be modified) do not presently give creative examples of EST utility. For instance, the sole example in the training materials of how the PTO might deal with an EST is frankly trivial enough to not really be a subject of controversy (i.e., the EST is only disclosed as a probe for an unknown gene).[61]

C. Single Nucleotide Polymorphism's (SNPs)[62]

The Guidelines do not address the utility of SNPs. It is possible to extrapolate from the Brenner v. Manson holding to suggest what might happen. One way to approach the problem is to take a position that SNPs are not patentable because the protein they express has no 'real world' utility' or, alternatively, that further research on the expressed protein is needed to discover a utility.[63] It follows that one should then look at what protein is expressed by the SNP. A SNP by itself, as a composition, would likely not be patentable unless it expresses a protein that has 'real world' utility. If, in attempting to patent a nucleic acid modified with a single substitution at position X, the claimed nucleic acid encodes a protein whose function is already known and can be predicted from the prior art (e.g., a "well established utility") or from the patent application itself and the polymorphism doesn't affect the encoded protein at all or affects it in a predictable way, then the SNP itself will probably be deemed patentably "useful". That is, the predictive nature of the art is such that if the function of the encoded polymorphism is known, the 'metes and bounds' can be defined, and it should pass the test. Nevertheless, even minor changes in DNA sequence can affect the structure and function of an encoded protein. If the specific polymorphism affects the encoded protein in an unknown or unpredictable way, then the function of the protein encoded by the SNP cannot be predicted and the claimed SNP would not encode a protein having any real world utility. Thus, the claimed SNP would not be "useful".

Other facts may lead to different results which may have little to do with what sort of protein is expressed by the polymorphism. Suppose a SNP does not encode a protein with any 'real world' utility but the particular polymorphism is already known, or discovered by the inventor, to always be present as a marker in some disease condition. In this situation, the knowledge that a disease condition is related to the SNP is sufficiently predictive of the SNP's use, that the specific polymorphism itself may have patentable utility as a method of use or composition, whether or not it encodes a protein that has a known function.

In short, the Guidelines tells inventors that they must be able to identify a 'real world' use for the claimed invention either in the prior art, or by clear support in the patent application, or by other evidence at the time of filing. This necessarily means that issues regarding the use of SNPs and ESTs for chromosome mapping, tissue typing or diagnostic markers will have to be resolved on a case-by-case basis.

D. Utility based on DNA/Protein Homologies

We have suggested that parts of the Brenner v. Manson holding and certain Federal Circuit decisions are consistent with a view that 'real world' utility is based upon the predictive nature of the prior art. Indeed, much of the criticism of the previous incarnations of these Guidelines came from federally-funded laboratories and academic research groups who were concerned about the apparent uncertainty in predicting gene and protein function from computer-based homology searches.[64] The PTO interpreted this to suggest that these groups would prefer a per se rule which says, in effect, ' a claimed DNA or protein has no patentable utility if such utility is based upon structural or sequence homology with a known DNA or protein.'

It is possible in biotechnology to find some recognizable counterpart to the concept of structural homology in organic chemical patent law, in which a measure of sequence similarity does suggest an expectation that there is functional equivalence.[65] Nonetheless, the key point made by the commentators to the prior Guideline versions was that structural identity in primary nucleotide or amino acid sequence, between a claimed DNA/protein and a DNA/protein found in an existing database, may not be sufficient to predict a function for the claimed DNA/protein. If we apply the Brenner v. Manson logic, this suggests that, because at present there are no general predictive relationships between DNA/protein sequence and functional activity, finding an asserted sequence homology to DNA in a database is not sufficiently predictive of use to allow the "metes and bounds of the monopoly [to be] capable of precise definition".[66]

The Guidelines modify this approach in an important way and will take into account " .. both the nature and degree of the homology".[67] Unless the PTO has reason to rebut an assertion of utility based upon homology, the PTO must accept the utility.[68] The safeguards against the unpredictable nature of the structure/function relationship are delineated in the three-part test, namely that the claimed DNA or protein must be asserted to have a specific, substantial and credible utility and this assertion must be based upon homology to existing DNA or protein also having a specific, substantial and credible utility. This will not satisfy the critics calling for a per se rule against finding utility from structural or sequence homology. Although it is premature to predict what might happen with any given factual situation, several practical points may be worth noting.

It appears that, even if one could predict the function of a claimed material from its sequence similarity with a material that is part of a known family of materials, the patentable utility of a homologue will depend in large part upon whether or not the existing family of known materials also passes the test of patentable "utility".[69] As alluded to above, this may well depend on the availability of information about the 'existing family'. We might imagine that a database exists of a family of proteins, but the database is private. Even if such private information could be used in the utility analysis,[70] the file history of an issued patent becomes publicly available and thus we may expect that there will be confidentiality and privacy concerns in this regard.

Furthermore, we note the instructive comparison between the nature of homologies in biotechnology[71] and the nature of the structure/function relationship in chemical patent practice. It is clear that DNA and proteins are considered 'chemicals' under the patent law.[72] Chemical patent practice has a well developed case law regarding the concept of 'structural obviousness".[73] The inventor of a chemical that is structurally similar to one or more members of a known family of chemicals must show that her structurally similar compound has some unexpected or nonobvious properties not predicted by knowledge of the properties of the 'genus' and/or that the changed structure of the claimed compound is not predicted by the prior art.[74]

The utility Guidelines in conjunction with chemical patent case law may result in claims that meet the utility condition, but ultimately are not patentable. Imagine that protein X of unknown biological activity is shown to have 90% sequence identity to protein Y that is a member of a cell surface receptor family whose biological function is known as being important in a disease. If the PTO decides that protein X is useful according to its three-part test, they may conclude that the protein is obvious (and thus not patentable) unless protein X has some properties not predicted by knowledge of the existing family of receptors. This is a very fact-specific inquiry. If protein X is an intracellular protein, it may be possible to argue that the (10%) difference in primary amino acid structure could not have been predicted by knowledge of the existing protein family, particularly since protein X is intracellular and protein Y is a cell surface receptor.

Generally, large pharmaceutical companies have tended to favor non-proteinaceous 'small molecules' that can be given as pills since many proteins are destroyed by passage through the gut . Thus, these companies view the genome and its associated proteins as targets against which to synthesize inhibitors or actuating molecules. It is an interesting question if it is actually easier in practice to show homology-based utility and non-obviousness for non-protein organic 'small molecules' than it is for

DNA or protein molecules.[75] This may make a difference in informing future strategic decisions about whether to spend resources in small molecule versus protein-based drug development.

BEYOND UTILITY

PATENTING "LIFE'

While the Guidelines give PTO examiners and patent applicants needed clarification on the utility criteria, the PTO, in response to commentator queries, neatly summarized the legal foundation of DNA and protein patents. The PTO asked, and answered, the most frequently cited arguments against 'gene patents' by invoking case law, legislative intent, and the U.S. Constitution. Patenting DNA sequences have been criticized on several grounds. We briefly summarize them below and provide comments.

- the cloning of a gene is a mere 'discovery' and not an invention and thus genes should not be allowed to be patented
- genes are natural materials and not human products of manufacture

The case law is clear that the dichotomy between 'invention' and 'discovery' is false. Section 101 of the U.S. patent code sets forth the concept of utility and lists the statutory subject matter that is patentable. A molecule, newly discovered and described, that meets the three-fold PTO criteria of novelty, utility and non-obviousness, is patentable subject matter.

Patents have been awarded on entities isolated from nature for nearly 100 years.[76] An excised gene qualifies for patent under the same grounds that any purified and isolated chemical compound is eligible for a patent. Comments (1) and (2) of the Guidelines[77] and the PTO response to them, are critical in this regard and serve as a clearly written summary by the PTO as to why recombinant DNA and proteins are legally protectable under U.S. patent law. In brief, the PTO reminds us that a biological material is patentable if it is in a purified or concentrated form and therefore not previously described. The PTO has awarded patents for extracts from glandular tissue (purified adrenaline) and microbes isolated from soil. The purified form of the substance distinguishes it from the form in which it occurs in nature. This key concept (or conceit, depending upon one's point of view) has developed, in part, from the so-called "purity" line of cases emanating from the U.S. Patent Office.78 Whether intended to be so or not, these comments are in effect, a public statement to critics of "patenting life". Such critics have repeatedly demanded an answer to the question, "Why should cloning a gene be an "invention" involved in isolating a novel molecule, instead of a mere 'discovery' of some body part already existing, and thus not patentable?.

- gene patents should be directed at methods of use and not to the DNA itself

The Supreme Court has ruled that a microorganism can be patented as a composition as well as for specific methods of use.[79] A patent on a composition of matter, even if based on a single use, gives the patent holder an exclusive right to bar others from using, that composition for any purpose.[80] When a new use is discovered for a patented DNA or protein, the inventor of the new use may qualify for a process patent, even if the DNA composition is already patented.[81] The new patent holder may be required to pay a licensing fee for the composition, while still holding a patent on a new process. The PTO asserts that a new use may qualify for its own process patent, "notwithstanding that the DNA composition itself is patented".[82] The presence of "dominating" patents leads to an access issue.[83]

- sequencing DNA is so routine that composition patents using such methods fail the test of 'non-obviousness'

The PTO, supported by the case law, does not consider the method of isolating DNA as relevant to the question of whether or not the composition itself is non-obvious.[84] Thus, a routine method can be used to discover a new material.

- non-coding gene sequences cannot meet a utility standard

The PTO has answered this question by requiring the sequence to have a substantial, 'real world' utility. There is no per se rule that non-coding gene sequences cannot meet the utility standard.

Nonetheless, the comments and the Guidelines wisely leave for other fora the difficult questions regarding the ethical and social manifestations of

cloning, patenting and experimenting with DNA.[85]

UTILITY AND ACCESS

Just as managing uncertainty was a key driver for the Brenner v. Manson quid pro quo,[86] so it is that quantifying and allowing for uncertainty also plays itself out after a patent issues, in the context of patent access. We have a few comments as they relate to the utility requirement discussed herein.

Access to patented tools that can be used in research is a difficult issue not resolved by the Guidelines. One could take the logical position under Brenner v. Manson that there is no such thing as a patented 'pure research' composition or method since, in order to be patented in the first place, its utility could not solely be as a discovery device. The patent statutes provide no literal language which would support any unlicensed use of a patented invention in research. Practically speaking, the concept will usually rear its head in infringement situations. One might find it hard to imagine that a patent holder would be willing to expend substantial litigation costs to put the patent at risk by bringing suit against a non-profit research laboratory or a university. In this regard, we note that in March 2000, Elan Pharmaceuticals announced it had sued the Mayo Foundation for patent infringement, alleging that Mayo was using certain patented transgenic mice without authority. The lawsuit was dismissed in June with a summary judgment of patent invalidity against Elan.[87] Increased ties between industry and research/academia may alter the legal landscape since more is at stake. Lawsuits like Elan's may happen more often. At present, a 'research exemption' is still probably an unwritten exemption for academics. Recent case law suggests a very narrow true research exemption, reserved for experiments conducted for amusement, to satisfy curiosity or for philosophical inquiry.[88] At present, adoption of a patented tool for use in an experimenter's business or with an aim to discover something of commercial utility (i.e., research motivated by a commercial purpose) will make the exemption unavailable

The access problem is related to utility in the following way. If society wants to encourage innovation in a particular field known to have a 'well established' utility (such as the field of transgenic mice carrying known, disease-related genotypic and phenotypic traits or the field of using SNPs as genetic markers of disease) and this field is exploited in the sense that materials are made, use and sold by those in the field, then such materials should be protected by patent. Problems will inevitably arise since adoption of an already 'useful' (i.e., patented) tool for purely experimental purposes and not with an aim to discover something of commercial utility (i.e., research motivated by a non- commercial purpose) raises different access issues than adoption of a patented tool for use in an experimenter's business or with an aim to discover something of commercial utility (i.e., research motivated by a commercial purpose).

One person's patented tool used in research is another's critical component in making a commercial product. For a patent owner, the issue becomes one of deciding how certain they can be of extracting value for a patented tool. For the end user, the issue often is one of quantifying the legal and business risk in not accessing the product. Thus patented reagents sold to end users will likely not be a bar to further research and development since a company would probably rather buy them than face a lawsuit or create them de novo.[89] In this case the patent owner is fairly sure of extracting value for the product and the patent user is certain that their costs are constrained. Patented materials are also routinely used for drug discovery or in quality assurance/quality control assays on pre-commercial or commercial products. Under these circumstances, the owner of a patented tool may place a different value upon her "reagent", depending upon the use. Thus, an end user may need to negotiate for a license to a drug discovery tool and, depending upon the license terms and the intent of the parties, this may increase the potential uncertainty of obtaining access and the cost to the end user. In the trivial case, it seems clear that giving exclusive rights to one user does risk inhibiting optimal use of tools and interferes with downstream incentives for product development. Just ask any Vice President of research or VP of Business Development who has had to stop a pre-clinical drug development program because a key tool has been exclusively licensed away or the overall royalty burden has become too high for commercialization.

We can summarize some of the real-world business decisions created in this regard by noting that computer generated homology searching can turn up many ESTs and putative full length coding regions, the proteins of which may have some therapeutic value. Seven hundred page patent applications, filed with hundreds of DNA sequences, are not uncommon. It is more likely than not that only a small percentage of these hundreds of sequences have real world biological function since their function is putatively based on sequence similarities to known DNA encoding known proteins. If an application such as this is to be published[90], the patentee can decide not to have it publish and keep all the sequences as a trade secret, let the PTO and the courts determine how to interpret the utility requirement, and then patent those sequences that pass the test. We note that if the application is not published, the patentee cannot complain if someone else independently discovers and patents the invention and blocks its use (by the patentee!). The law of trade secrets does not protect a secret against independent development.[91] The advantage of publishing these sequences anyway is that the publication will serve as novelty-destroying prior art to block others from patenting the same sequences. Another, more subtle advantage, will be that publication exacerbates the uncertainty of the competition. A competitor faced with a patent application containing these (possibly) statutorily 'useless' DNA sequences, must make a difficult judgment and quantify the likelihood that, for instance, "sequence number 346" will not issue as a composition. This is something that won't be known for many years. Should the competition make the investment now and hope that "sequence 346" never gets issued? Should they design an alternate form of the sequence? Should they forgo obtaining an exclusive position on a composition and go after diagnostic or therapeutic method of use exclusivity?

CONCLUSIONS

The Guidelines are designed to provide greater uniformity and consistency with regard to the utility requirement for determining patentability. They attempt to accomplish this by creating a presumption of utility which the PTO has to overcome and by creating a three-part test. Under the traditional Brenner v. Manson standard, it seems doubtful whether many EST or SNP sequences would be found to have 'utility'. The PTO has, however, added a requirement that the inventor show a 'credible' utility. This anchors the three-part test in a consideration of whether a person having ordinary skill in the art would accept that the invention is available for such use as of the time of filing. This consideration hinges on the level of skill of the ordinary practitioner in molecular biology, which is quite sophisticated. We may be surprised to see how many DNA, protein, EST or SNP inventions have "credible" utility.

At present, patent practitioners and inventors should provide evidence that the claimed invention would have a use that is supported by the as-filed patent application or they should submit evidence that the use would have been 'well established' as of the filing date. The ideal situation is for biotechnology patent applications to include various functional analyses of the DNA or actual expressed protein in order to be more certain of overcoming the utility test.

The PTO's desire to clarify the legal requirements and attempt to increase the predictability of results based on this clarification have been generally well received and are to be applauded. It is, however, too early to tell if the Guidelines solve the problems they have set out to solve.Major uncertainties will not be clarified for some time. In particular, the issue of obtaining utility from a consideration of structural/sequence homology will likely become more important in the near term. If the PTO follows its case law with regard to the doctrine of 'structural obviousness' developed from organic chemical practice, it may well be that many DNA and protein composition claims, though 'useful' will fail as being "obvious' over the structurally related prior art. The ability to overcome this failure by showing some unexpected properties of the DNA or protein must be taken on a case-by-case basis. The surprisingly few number of human genes (as compared to, for example, the mouse) makes it likely that it is the proteins encoded by the genes that are responsible for the diversity that makes us biologically 'human'.[92] It may be that most of these human genes have already been published, filed as patent

applications or issued as patents. The ability to show an 'unexpected property' of a protein, against the backdrop of a multitude of possibly homologous proteins expressed by the 'small' number of human genes, will become increasingly important.

Other critical unresolved issues going forward will probably center on access to patented biotechnology inventions. There have been several suggestions made for dealing with these issues of access, briefly summarized below. One solution is to create a true research exemption from infringement.[93] It is hard to imagine how such an exemption would not devalue patents on research tools. Development of research tools is a lucrative business- just spend some time in a top research laboratory or biotechnology company. The line between basic research and commercial activity is already blurred. Where there is money to be made by developing and marketing research tools, any broad exemption from liability will deter private industry from developing them.

Another solution is to overrule Brenner v. Manson legislatively and return to a per se rule of utility[94] or the weaker "Story" rule.[95] It is argued that since the 'best' utility does not need to be disclosed, the lower bar of the Story utility is appropriate.[96] The obvious problem with these solutions is that it might flood the system with patents, increase litigation, and force licensing of trivial patents.

A third solution is to limit the scope of claims to just that utility that is described and sufficiently supported by data in the patent application. This is probably the easiest from a practical view point and it does not require overruling of Brenner v. Manson. In fact, it is done all the time in the day-to-day practice of the PTO based upon the other statutory requirements for patentability, the "written description" and "enablement" sections.[97]

It is clear that access to biotechnology inventions presents significant issues. Indeed, a solution has been suggested recently by the PTO itself. On January 19, 2001 the PTO published a position paper designed to stimulate thinking about access.[98] The article suggests that agreements between several patent owners to collectively license their IP to interested parties (i.e., "patent pooling") may be one way of attacking the problem.

In the final analysis, it is difficult to separate the questions of utility and access. In a world where several inventions of different statutory class may arise from a single DNA or protein sequence and where many therapeutic genes are already in the public domain or have been filed upon, business people and investors will still need to make difficult decisions about whether to attain patent exclusivity for statutorily " useful" methods rather than run the risk of trying to obtain patent protection for a DNA or protein compositions. The PTO response to queries and criticisms regarding the legal and ethical grounds for gene patents provides little solace to critics who feel that there have been quantum jumps in patent policy that departed from the legislative history. The PTO's review of the law and rationale make the case for allowing the patenting of DNA and proteins more convincing that some critics have been willing to accept. Thus, in clarifying the criteria for 'utility', the PTO is signalling that the impetus to change the ground rules for gene patents or patents on living organisms, or to change the rules on issues such as establishing a research exemption, must arise from Congress and not the Patent Office.

ENDNOTES

1. Notice, Utility Examination Guidelines, United States Patent and Trademark Office, 66 Fed. Reg. 1092-1099 (Jan. 5, 2001) .
2. Id. at 1092-1097 (twenty three comments by third parties and corresponding PTO responses).
3. Legal Analysis Supporting Utility Examination Guidelines, available at http://www.uspto.gov/web/offices/pac/dapp/oppd/utility.htm. See also USPTO Training Materials for Revised Interim Utility Guidelines, March 7, 2000 republished by Patent Resources GroupÆ, Charlottesville, VA (hereinafter "Training Materials").
4. 35 U.S.C.ß 101 (1994). See also infra note 7 and accompanying text.
5. 383 U.S. 519, 86 S. Ct. 103, 16 L.Ed.2d 69, 148 USPQ 689 (1966).
6. Guidelines, supra note 1 at 1096 (comment (19) dealing with utility based on computer analysis to assign function to homologous nucleic acid sequences).
7. 35 U.S.C.ß 101 (1994).
8. U.S. Constitution, Art. I, ß 8, cl.8.
9. 15 F. Cas. 1018 (C.C.D. Mass 1817).
10. Id. at 1019.
11. 383 U.S. 519 (1966) .
12. Id. at 539 n.3 (until 1950, PTO practice to grant chemical compound patent claims although no use was stated and description in application was very broad) (J. Harlan, dissenting opinion). Accord, In re Joly, 376 F.2d 906, 915-917, 153 USPQ 243-266 (C.C.P.A. 1967) (Smith, J. dissenting).
13. 333 F.2d 234, 142 USPQ 35 (C.C.P.A. 1964), cert. granted, sub nom. Brenner v. Manson, 383 U.S. 519 (1966).
14. 333 F.2d at 235, 142 USPQ at 36.
15. 383 U.S. at 519, 521-22 (summarizing assertions of Manson).

16. 333 F. 2d at 235, 142 USPQ at 36. See also 383 U.S. at 521 (summarizing procedural posture of case prior to granting certiorari). See also 35 U.S.C. ß 135 (1984) (interference statute dealing with 'priority' contest between two different patent applications, or an issued patent and an application, that simultaneously claim the same invention).

17. 333 F.2d at 238, 142 USPQ at 38 (process operates a claimed and produces the intended result). See also Commonwealth Engineering Co. v. Ladd, 199 F. Supp. 51, 53, 131 USPQ 255, 257 (D.D.C. 1961), citing Isenstead v. Watson, 157 F. Supp 7, 9, 115 USPQ 408, 409-410 (D.D.C. 1957) (for a composition, the utility test is whether compound will operate as disclosed and claimed; for process, test is whether it operates as claimed and produced the intended result). This holding actually extends Justice Story's minimal threshold. Supra note 9, and may be the origin of the 'operability' line of cases. See, e.g., Raytheon Co. v. Roper Corp., 724 F.2d 951, 958, 220 USPQ 592, 598 (Fed. Cir. 1983) (invention must be operative for at least one stated objective to possess utility).

18. 383 U.S. at 536.

19. Id. at 531-36.

20. Id. at 534.

21. Id. at 534-35.

22. See, for example, In re Kirk, 376 F. 2d 936, 947, 950-53, 153 USPQ 43, 266-281 (C.C.P.A. 1967) (Rich, J. dissenting); In re Joly, 376 F.2d at 909, 915, 153 USPQ 243,262 (impossible to define criteria for something 'useful and judges should not be arbiters of utility). For legal commentary, see, e.g., Lawrence R. Velvel, A Critique of Brenner v. Manson, 49 J. Pat. Off. Soc'y. 5 (1967); Eric P. Mirabel, "Practical Utility" is a Useless Concept, 36 Amer. U. L. Rev. 811 (1987). See generally Phanesh Koneru, To Promote the Progress of Useful Art[icle]s?: An Analysis of the Current Utility Standards of Pharmaceutical Products and Biotechnological Research Tools, 38 IDEA 625, 642 n.76 (1998) and references cited therein.

23. Donald S. Chisum, CHISUM ON PATENTS, A TREATISE ON THE LAW OF PATENTABILITY, VALIDITY AND INFRINGEMENT, at ß 4.02 [2] [c] [ii] , Lexis Publishing (2000) (hereinafter "Chisum").

24. See, e.g., In re Zeigler, 999 F.2d 1197, 26 USPQ2d 1600 (Fed. Cir. 1993); Cross v. Iizuka, 753 F.2d 1040, 1044, 224 USPQ 739, 744 (Fed. Cir. 1985) (invention is not patentably useful unless substantial and practical utility has been discovered); Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (C.C.P.A. 1980).

25. 753 F.2d at 1040, 224 USPQ at 739.

26. 753 F.2d at 1044, 224 USPQ at 743.

27. 753 F.2d at 1051, 224 USPQ at 748.

28. 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

29. Id. at 1566-67, 34 USPQ2d at 1441, citing with approval Rey-Bellet v. Engelhardt, 493 F.2d 1380, 181 USPQ 453 (C.C.P.A. 1974) (evidence of success with structural homologues is relevant in determining if utility is credible).

30. 51 F.3d at 1567, 34 USPQ 2d at 1442.

31. Id.

32. Id. at 1568, 34 USPQ2d at 1442.

33. Id. (emphasis added).

34. See Koneru, supra note 22 at 656, citing In re Papesch, 315 F.2d 381, 137 USPQ 43 43 (C.C.P.A. 1963) for support of the idea that chemical intermediates with biological activity should be treated the same as pharmaceuticals. 315 F.2d at 391, 137 USPQ at 51 (from patent law standpoint, chemical cannot be separated from its properties).

35. Biotech Industry Blasts PTO at San Diego Hearing, 48 Pat. Trademark & Copyright J. 677, 677 (BNA) (1994).

36. Guidelines for Examination of Application for Compliance with the Utility Requirement, 60 Fed. Reg. 36263-02 (July 14, 1995).

37. Revised Interim Guidelines for Examination of Patent Application under 35 U.S.C. ß 112, ∂ 1, "Written Description Requirement", 64 Fed. Reg. 71427 (Dec. 21, 1999).

38. Revised Interim Utility Examination Guidelines, 64 Fed. Reg. 71440 (Dec. 21, 1999), correction at 65 Fed. Reg. 3425 (Jan. 21, 2000).

39. Guidelines, supra note 1 , ß II B at 1098.

40. If the patent applicant asserts no utility but there is a 'well established' utility (one in which a PHOSITA would understand why the invention is useful and that it is specific, substantial and credible) then the claimed invention passes the utility test. Guidelines, supra note 1 at 1098, ∂ B 1 [(a) - (c)]. If the patent applicant does assert a "practical" utility (presumably passing the Brenner v. Manson test) and the assertion is credible as measured by a PHOSITA at the time of filing, the claimed invention also passes the utility test. Guidelines, supra note 1 at 1098, ∂ B 2 (a) [(1) - (2)]. In this case, a "well established' utility appears irrelevant. If assertions of utility are not credible and there is no 'well established' utility, the claims are to be rejected. Guidelines, supra note 1 at 1098, ∂ B 2 (b). Query: if there happens to be a 'well established' utility, the invention would presumably pass the utility test, notwithstanding the fact that the inventor's assertions of utility were not credible.

41. Guidelines, supra note 1 at 1098, ∂ B 2 (c) [(1) - (2)].

42. Guidelines, supra note 1 at 1098, ∂ B 3. Where the asserted utility is not 'specific or substantial', the PTO must establish by a preponderance of the evidence (i.e., more likely than not) that a PHOSITA would not consider the asserted utility to be specific and substantial. In addition, the PTO has to also show why the asserted utility is not 'well established". Guidelines, supra note 1 at 1098, ∂ B 3 (a) [(1) - (3)]. Where the asserted utility passes the 'specific and substantial' test but is not credible, the PTO must establish by a preponderance of the evidence, that a PHOSITA would not consider the utility credible. Guidelines, supra note 1 at 1098, ∂ B 3 (b) [(1) - (3)]. Query how difficult it will be to prove a negative.

43. Guidelines, supra note 1 at 1099, ∂ B 4.

44. Brenner v. Manson, 383 U.S. at 536.

45. Training Materials, supra note 3 at 5. See also Legal Analysis, supra note 3 at 6-7 (utility credible unless logic is 'seriously flawed").

46. In re Brana, 51 F.3d at 1566, 34 USPQ2d at 1441 (evidence presented by PTO did not cause person having ordinary skill in the art to question the asserted utility of claimed compounds). But see David G. Perryman and Nagendra Setty, The Basis and Limits of the Patent and Trademark Office Credible Utility Standard, 2 J. Intell. Prop. L. 509, 529 (discussing origins of 'credible" utility standard of the 1994 guidelines and asserting that the term 'credible' is not found in prior federal case law).

47. Guidelines, supra note 1 at 1096 (comment (19)).

48. 383 U.S. at 532 (Court does not overturn PTO's requirement of showing a sufficient likelihood that claimed steroid would have same activity as homologue).

49. 35 U.S.C. ß 282 (every issued U.S. patent is presumed valid).

50. In terms of the three-part test, the Guidelines make no distinction as to whether the 'existing nucleic acids or protein' (i.e., members of the class of compounds) are in private or public hands. It may be an interesting question as to whether this lack of distinction will be important in a utility analysis. If a class of proteins is being compared via homology to a protein in a patent claim, the answer to the question of whether members of this protein class share a specific, substantial and credible utility, see Guidelines, supra note 12 at 1096 (comment (19)), will arguably be more difficult to answer if the class of proteins is in private hands and not available to the public. Note that in other patent contexts, knowledge or use can only be used as "prior art" if available to the public. See Carella v. Starlight Archery, 804 F.2d 139,139, 231 USPQ 644, 646 (Fed. Cir. 1986) (to destroy novelty of a patent claim, knowledge or use must be available to the public). See also, 35 U.S.C. ß 102 (g) (1994) (patents not awarded if invention also made in the U.S. by someone else who did not suppress or conceal it); Chisum, supra note 23 at ß 3.05 920 [a] (discussing ß 102 (g) of the U.S. patent code). There may, of course, be non-patent related concerns with using a private database.

51. In re Hafner, 410 F.2d 1403, 1404-05, 161 USPQ 783, 785 (C.C.P.A. 1969) (prior compound lacking any utility can destroy novelty of a claimed compound); In re Schoenwald, 964 F.2d 1122, 1123, 22 USPQ2d 1671, 1672 (Fed. Cir. 1992) (a novelty-destroying reference does not have to disclose a use).

52. Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, 1551, 13 USPQ 2d 1301,1304 (Fed. Cir. 1989) (even if a reference discloses an inoperative device, it is prior art for all that it teaches); Symbol Technologies v. Opticon, Inc., 935 F.2d 1569,1578, 19 USPQ2d 1241, 1247 (Fed. Cir. 1991) (reference that lacks any description of how to make and use may qualify as prior art for determining obviousness), citing Reading & Bates Construction Co., v. Baker Energy Resources Corp., 748 F.2d 645,652, 223 USPQ 1168, 1173 (Fed. Cir. 1985).

53. Rey-Bellet & Spiegelberg v. Engelhardt, supra note 28 at 1383, 181 USPQ at 454-55 (in an interference proceeding, evidence can show 'substantial utility' for any purpose); cf. Scott v. Finney, 34 F.3d 1058, 1062-63, 32 USPQ2d 1115, 1119-20 (Fed. Cir. 1994) (to show that claimed invention was made and used, testing must show reasonable utility based on problem to be solved).

54. 149 F3d 1368 (Fed. Cir. 1998), cert. denied, 142 L.Ed 2d 704 (1999).

55. Id. at 1373. (patented method produced a useful, concrete and tangible result). See

also AT&T Corp. v. Excel Communications, Inc., 172 F.3d 1352, 1358, 50 USPQ2d 1447, cert. denied 120 S. Ct. 368 (1999) (Fed. Cir. 1999) (claims to process embodied in algorithm for billing telephone calls produced a useful, concrete and tangible result).

56. Examination Guidelines for Computer Related Inventions, 1184 Off. Gaz. Pat. Off. 87 (Mar. 26, 1996), Section IV.B.2 (b) (i), available at http://www.uspto.gov/web/offices/pac/compexam/examcomp.htm. See also Manual of Patent Examining Procedures ("MPEP") ß 2106 at 2100-15, (7th Ed., July 1998) available at http://www.uspto.gov/web/offices/pac/mpep/index.htm (no explicit manifestation of a tripartite utility test for computers). See also Stephen G. Kunin, Patent Eligibility in View of State Street and AT&T v. Excel Communications, 2000 Intell. Prop. L. Rev. 61 (2000) (questioning if the Federal Circuit utility test is helpful).

57. Training Materials, supra note 3 at 6.

58. ESTs are partial DNA 'coding' sequences, typically 150-400 base pairs long and are often obtained by partial sequencing of random clones from DNA sets that lack non-protein coding DNA portions.

59. Guidelines, supra note 1 at 1095 (comment (14)).

60. Id.

61. Training Materials, supra note 3 at Example 9.

62. SNPs are single nucleotide polymorphisms: a mutation event in which a single nucleotide of a DNA changes into a different nucleotide. A purine nucleotide changing into another purine (or a pyridimine nucleotide changing into another pyrimidine) is called a 'transition", whereas a purine changing into a pyrimidine (and vice versa) is called a 'transversion".

63. See, e.g., 383 U.S. at 535, 148 USPQ at 696 (a product has no patentable utility if its only use is as an object of further research).

64. See Public Comments on the United States Patent and Trademark Office "Revised Interim Utility Examination Guidelines", 64 Fed. Reg. 71440, Dec. 21, 1999, corrected Fed. Reg. 3425, Jan 21, 2000 at http://www.uspto.gov/web/offices/com/sol/comments/utilguide/index.html.

65. In re Mayne, 104 F.3d 1339, 1342-43 , 41 USPQ2d 1451-53 (Fed. Cir. 1997) (modified protein obvious in view of references suggesting structurally similar proteins). See also In re Dillon, 919 F.2d 688, 693, 16 USPQ2d 1897,1901 (Fed. Cir. 1990) (in banc), cert. denied, Dillon v. Manbeck, 111 S. Ct. 1682 (1991) (structural similarity between claimed composition and prior art creates presumption of obviousness).

66. 383 U.S. at 534-35.

67. Guidelines, supra note 1 at 1096 (comment (19)).

68. Guidelines, supra note 1 at 1096 (comment (19)).

69. Guidelines, supra note 1 at 1096 (comment (19)).

70. See supra note 50.

71. See supra note 65.

72. In re Deuel, 51 F.3d 1552, 1557, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995) (DNA claims at issue are to a 'chemical entity').

73. See also supra note 65. See Guidelines for the Examination of Claims Directed to Species of Chemical Composition Based Upon a Single Prior Art Reference, 63 Fed. Reg. 47001 et seq. (Sept. 3, 1998) and references cited therein, available at http://www.uspto.gov/web/offices/com/sol/notices/fr980826.htm [hereinafter "Species Guidelines"]

74. Species Guidelines, supra note 73 and references cited therein. See also In re Papesch, 315 F.2d at 391, 137 USPQ at 51 (presumption of obviousness from existing homologue rebutted by showing unexpected properties of claimed compound).

75. Andrew Pollack, Drug Developed from Gene Study Tested on People, The New York Times, Feb. 26, 2001, available at http://www.nytimes.com/2001/02/26/business/26DRUG.htm (GlaxoSmithKline drug likely to be the first 'small molecule' drug developed from genetic database searching has entered clinical trials)

76. See, e.g., Parke-Davis-Co. v. H.K. Mulford Co., 189 F. 95, 103 (S.D.N.Y 1911) (even an extracted product could be patented). The PTO has awarded patents for extracts from glandular tissues and microorganisms isolated from soil. Guidelines, supra note 1 at 1093 (comment (2)) and references cited therein.

77. Guidelines, supra note 1 at 1092-93.

78. In re Bergstrom, 427 F 2d 1394, 1401, 166 USPQ 256, 262 (C.C.P.A. 1970) (pure materials are by definition novel as compared to impure materials); See also In re Seaborg, 328 F.2d 993, 996, 140 USPQ 659, 661 (C.C.P.A. 1965) (Glenn T. Seaborg's purification of element 95 patentable since prior work could only have made virtually undetectable amounts). See also Guidelines, supra note 1 at 1092-93 (when the patent issued for purified adrenaline about 100 years ago, people did not infringe the patent merely because their bodies naturally included unpurified adrenaline).

79. Diamond v. Chakrabarty, 447 U.S. 303, 309 (1979) (live, human made microorganisms are patentable).

80. 35 U.S. ß 271 (unauthorized use of a patented product is an infringement).

81. 35 U.S. ß 101 (patent awarded on 'improvement' to methods, process or compositions).

82. Guidelines, supra note 1 at 1094-95 (comment (7) and (12)).

83. See infra and accompanying text (summarizing access issues).

84. See In re Deuel, 51 F.3d 1552, 1558, 34 USPQ 2d 1210, 215 (Fed. Cir. 1995) (claims to specific DNA not made obvious merely because methods for generating the DNA are known).

85. Andrew Stern, "Scientists Say Team will Use Clones to Help the Childless", Boston Globe, Jan. 27, 2001 at A7 (international group plans use husband's undifferentiated stem cells and insert its DNA into wife's egg stripped of its genetic material); Emma Ross, House of Lords OKs Embryo Cloning, Wash. Post, Jan. 23, 2001 at http://www.washingtonpost.com/ac2/wp-dyn/A34105-2001Jan23.htm.

86. 383 U.S. at 534-35.

87. See Rex Dalton, Patent Suit on Alzheimer's Mouse Rejected 405 Nature 989, 989 (June 29, 2000) (summarizing June 15, 2000 ruling that Elan's patents were invalid and thus not infringed although Elan intends to appeal). If one doesn't think research tools are big business, consider that breeding trios of the Mayo Foundation transgenic mice are purportedly sold for $850,000. Rex Dalton, Researchers Caught In Dispute Over Transgenic Mice Patents, 404 Nature 319, 320 (March 23, 2000) .

88. Roche Prods. Inc., v. Bolar Pharmaceutical Co. Inc., 733 F.2d 858, 863, 221 USPQ 937, 940 (Fed. Cir. 1984), cert. denied, 469 U.S. 856 (1994) (experimental use doctrine did not cover defendant's business use of patented drug, but it would have for "... amusement, to satisfy idle curiosity or for strictly philosophical inquiry.") See also M. Patricia Thayer and Richard A. De Liberty, The Research Exemption to Patent Infringement: The Time has Come for Legislation, 4 J. Biolaw & Bus. 1, 6 (2000) and references cited therein (Congress should balance the competing interests in protecting research conducted on new discoveries) available at http://www.hews.com/news/articles/infringe.pdf.

89. The threat of a lawsuit carries with it the issue of damages, a subject beyond the scope of this Article. There is little federal case law on the subject of damages for infringement of biotechnology research tools. Briefly, statutory law (35 U.S.C. ß 284 (1984) stipulates that damages must compensate for infringement but cannot be less than a 'reasonable royalty' for use made of the invention. It is suitable to consider royalties paid by others in the industry for use of a comparable patent. American Original Corp. v. Jenkins Food Corp., 774 F.2d 459, 464, 227 USPQ 299, 302 (Fed. Cir. 1985). What are the damages for use of a reagent/research tool? The danger that an aggrieved plaintiff will look at royalties on sales of final product developed, tested or optimized using a patented research tool cannot be dismissed. See James G. Cullen, Panning for Biotechnology Gold: Reach-Through Royalty Damages Awards for Infringing Uses of Molecular Seives:, 39 IDEA 553, 566 (1999) (summarizing law of damages in biotechnology and noting a lack of federal case law).

90. See Changes to Implement Eighteen Month Publication of Patent Applications, 65 Fed. Reg. 57024 (Sep. 20, 2000), available at http://www.uspto.gov/web/offices/com/sol/notices/chpatapp.pdf . Certain provisions of the American Inventors Protection Act of 1999 (P.L. 106-113, 113 Stat. 1501 (1999)) provide for publication of U.S. patent applications to bring U.S. practice in line with European practice. With certain exceptions, patent applications shall be published eighteen months from the earliest U.S. filing date. 35 U.S.C.ß 122(b). A U.S. patent application does not have to be published but the patent applicant must certify that she won't file the application in another country that does have an 18 month publication period, although this may be rescinded under certain circumstances. See 35 U.S.C. ß 122 (b) (2) (B) (i)- (v). This means that a U.S. patent application could still be kept out of publication but only if the U.S. is effectively the only country in which the application is reviewed. Nonetheless, under certain circumstance, a U.S. applicant can file in the U.S. and then file overseas with a version that is less extensive and have a redacted version published. 35 U.S.C.ß 122 (b) (2) (B) (v).

91. Roger M. Milgrim, MILGRIM ON TRADE SECRETS, , vol. 2, at ß 7.02 [1] [a] and accompanying text (genuine independent development a complete defense; no protection to first user as against an honest discoverer), Lexis Publishing (2000) .

92. The human genome contains about 30,000 distinct genes. J. Craig Venter et al., The

Sequence of the Human Genome, 291 Science 1304 (2001). Estimates from genes analyzed to date suggest that the average number of alternate protein 'messages' per gene is 3-4 or more. This means that there are estimated to be 90,000 or more proteins encoded by the human genome. Id.

93. See Thayer and De Liberty, supra note 88 at 7 (Congress should exempt research from infringement).

94. See In re Kirk, 376 F.2d at 959, 153 U.S.P.Q at 275 (Rich, J., dissenting) (the best rule is that chemical compounds are per se useful); Koneru, supra note 22 at 668 and accompanying text (summarizing economic value of per se rule).

95. Konera, supra note 22 at 668-69. See e.g., In re Kirk, 376 F.2d at 957, 153 USPQ at 275 (Rich, J., dissenting) (Congress should provide that chemical compounds have utility per se).

96. Koneru, supra note 22 at 666 nn.220-23 and accompanying text (if a product with a trivial use can be patented under current U.S. practice, why not allow a product that satisfies the Story "minimal use" standard).

97. 35 U.S.C. ß 112, ∂ 1 (1994) (requiring disclosure sufficient to enable making and using claimed invention and for sufficient for written description supporting the claimed invention).

98. Jeanne Clark, Joe Piccolo, Brian Stanton, Karin Tyson, Mary Critharia, Stephen Kunin, Patent Pools: A Solution to the Problem of Access to Biotechnology Patents? (Dec. 5, 2000), at http://ww.uspto.gov/web/offices/pac/dapp/opla/patentpool.pdf.