

United States of America

Q150

**Patentability Requirements and Scope of Protection of Expressed Sequence Tags (ESTs), single Nucleotide Polymorphisms (SNPs) and Entire Genomes**

**1. Public Policy**

*A. Are ESTs, SNPs and genomes inventions, the patenting of which is contrary to "ordre public" or morality (TRIPS, Article 27.2)?*

**Answer**

Article 27.2 of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) provides:

Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their laws.

One of the principal functions of the patent system is to encourage investment in research and development. The U.S. Constitution recognizes the public benefits of the patent system in promoting the progress of science and the useful arts. U.S. Const. Art. I, Sec. 8, Clause 8.

It is generally recognized that the public interest is served by providing an incentive to those engaged in genetic research. Such research offers the potential for the discovery of diagnoses and therapies for genetic diseases, cancer and other human afflictions. Research of plant and animal genetics offers the potential for improved agricultural efficiencies. The arguments that DNA is common property and that DNA sequences are fixed and thus difficult to design around would apply equally to other biomolecules. For example, the structures of hormones, enzymes, polypeptides, receptors and the like are fixed in nature and, like DNA, often cannot be altered significantly without sacrificing activity. The patent system has provided a strong incentive for the research leading to the discovery of many biomolecules. The patenting of these biomolecules has not adversely affected the ordre public or morality. To the contrary, the protections provided by the patent system have led to the commercial availability of life-saving drugs and therapies.

Similarly, it should be expected that patenting of ESTs, SNPs and genomic DNA will benefit the public, by providing an incentive for this research. Accordingly, the patentability of such inventions and discoveries is not inconsistent with Art. 27(2) of TRIPS. Indeed, prohibiting such patenting may well be a violation of Art. 27(1), which requires that member states provide patent protection in all fields of technology.

A caveat, however, may involve claims to the human genome. A widely-publicized application claiming part-human chimeras, filed by a New York Medical College biology professor and Jeremy Rifkin, a vocal anti-biotechnology activist from Washington D.C., is pending before the United States Patent and Trademark Office ("USPTO"). On April 1, 1998, the USPTO issued a press release addressing the application (<http://www.uspto.gov/web/offices/com/speeches/98-06.htm>). Falling short of acknowledging the existence of the application (pending applications are, by U.S. law, maintained in secrecy by the USPTO), the USPTO noted that "inventions directed to human/non-human chimera could, under certain circumstances, not be patentable because, among other things, they would fail to meet the public policy and morality aspects of the utility requirement."

Recently, USPTO officials have commented in greater detail. It has been indicated that the USPTO would regard patent claims which "embrace a human" as violative of the Thirteenth Amendment to the U.S. Constitution, which prohibits slavery. *See, New Scientist*, June 26, 1999. A claim to a human genome, i.e., the entire DNA of an individual - even if novel and unobvious - could, according to this USPTO position, violate the Constitutional prohibition and thus be unpatentable. Where, as in the case of chimeras, the claimed invention comprises more than human genetic material, the USPTO's position is less clear. In U.S. Patent No. 5,602,307, claims directed to a transgenic mouse comprising alleles of the human CD18 gene were granted to the Baylor College of Medicine. The

Rifkin et al. chimera claims, however, encompass more human DNA than a single gene and have been rejected as "embrac[ing] a human being." See, *Legal Times Special Report: Intellectual Property*, August 16, 1999. So far, the USPTO has not provided any guidance regarding the amount of human DNA that must be present to render claims unpatentable because they "embrace a human being."

*B. Are patent offices the correct place to determine these questions and do they have sufficient resources to make such decisions?*

**Answer**

As discussed above, the USPTO has already determined that claims to human beings are prohibited both Constitutionally and "because, among other things, they would fail to meet the public policy and morality aspects of the utility requirement." The USPTO finds support for the "public policy and morality aspects of the utility requirement" in *Lowell v. Lewis*, 15 Fed. Cas. 1018, No 8568 (C.C. Mass. 1817) (Story, J.), quoted in *Tol-O-Matic Inc. v. Proma Produkt-und-Marketing GmbH*, 945 F.2d 1546, 1552 (Fed. Cir. 1991). In an analogous setting, the USPTO has authority to reject applications for the registration of trademarks that are deemed to comprise "immoral, deceptive, or scandalous matter." 15 U.S.C. § 1052(a). Accordingly, there is precedent for vesting the USPTO with the authority for resolving such public policy questions.

Whether patent offices have the resources and expertise for making such decisions is questionable. Patent examiners generally do not have specialized training in bioethics or related fields, and patent offices usually do not employ bioethicists. Moreover, ex parte patent prosecution does not afford an opportunity for members of the public to raise ethical concerns.

A persuasive argument can be made that patent offices should not attempt to regulate morality through the examination process. Under current law, no statutory provision explicitly gives the USPTO authority to reject patent claims on ethical or morality grounds. Section 101 of the patent statute defines patentable subject matter. Any decision that certain categories of subject matter encompassed within Section 101 are not patentable on public policy or morality grounds should be made by the Congress through normal legislative procedures.

**2. Utility**

*What level of utility should be required of patents for ESTs, SNPs and genomic DNA?*

**Answer**

The question of whether the requisite utility for patentability exists is probably different for ESTs, SNPs and genomic DNA. For example, DNA molecules representing SNPs are, at a minimum, useful for genotyping and thus may have value in forensic applications or paternity determinations. If the polymorphism is associated with a known trait or genetic disorder, then the DNA may be useful in diagnostic or therapeutic applications, or, in the case of plants or animals, in breeding programs. Similarly, genomic DNA, at a minimum, would be useful for identifying an individual, and thus potentially valuable in forensic applications or paternity determinations.

ESTs, on the other hand, present unique utility issues. The sequence of an EST represents a portion of a coding sequence from a gene that is transcribed by the organism and therefore presumably has some function. Typically, the function of the gene from which the EST was derived is unknown. Therefore, the EST does not have a specific utility. As a consequence, there has been much debate about the patentability of ESTs.

The National Institutes of Health ("NIH") was apparently the first to file patent applications on ESTs. These patent applications arose out of the work of then NIH scientist, Dr. Craig Venter, who was involved in the human genome sequencing project. The NIH has stated that it filed patent applications on these sequences as a defensive measure to preclude others from patenting and dominating the field. The USPTO rejected the NIH patent applications for, among other reasons, lack of utility. The NIH later abandoned these patent applications and now advocates against patentability for ESTs or partial DNA sequences for which there is no known function. The agency has indicated that it believes that such patents will interfere with basic research.

While initially rejecting the claims of the NIH applications, the USPTO has recently made an administrative

decision to allow patent claims to ESTs, provided that no more than ten unrelated sequences can be claimed in a single application. *New Scientist*, February 22, 1997; *Biotechnology Newswatch*, March 3, 1997. This decision was announced by Mr. Lawrence Goffney, who was then a Deputy Commissioner of Patents. The decision has also been discussed in public correspondence between Dr. Harold Varmus, Director of the NIH, and former USPTO Commissioner Bruce Lehman. See *F-D-C Reports - "The Pink Sheet,"* May 12, 1997, p. T&G-7. The USPTO justifies its decision to allow such claims on the grounds that ESTs have utility as probes for, e.g., mapping the genome. See article by John J. Doll, director of Biotechnology Examination USPTO in *Science*, 280: 689-90, May 1, 1998.

U.S. patent law requires that a patented invention be "useful." 35 U.S.C. § 101. There is an argument that an EST for which the only disclosed utility is as a probe for further research does not meet the statutory utility requirement. In the late 1960's the United States Supreme Court issued its decision in the case of *Brenner v. Manson*, 383 U.S. 519 (1966). This case remains the principal authority for applying the utility requirement of the patent laws. In the *Brenner* case, the applicant sought a patent on a novel steroidal compound. The applicant did not disclose a specific utility for the compound, but stated that it would be useful for further research in view of interesting biological activities of closely related compounds. The Supreme Court rejected this argument, holding that patentability required disclosure of a practical utility -- not merely a use for further research.

The effect of the *Brenner* decision was discussed in two important decisions of the Court of Customs and Patent Appeals ("CCPA"), *In re Kirk*, 376 F.2d 936 (C.C.P.A. 1967) and *In re Joly*, 376 F.2d 906 (C.C.P.A. 1967). The CCPA was a predecessor of the Court of Appeals for the Federal Circuit, the court that now hears all patent appeals in the United States. In the *Kirk* and *Joly* decisions, the CCPA considered the patentability of claims to chemical intermediates and chemical processes useful for making a product. In each case, there was no disclosed practical utility for the final product. The patent applicants argued that the inventions were patentable, because they served their stated purpose, i.e., the production of the desired product. A divided CCPA rejected these arguments. The court held that under the *Brenner* decision, the final product must have a stated practical utility. The CCPA majority acknowledged that the claimed inventions would have been patentable under its precedent prior to *Brenner*, but that *Brenner* had implicitly overruled that precedent.

Under the rationale of the *Brenner*, *Kirk* and *Joly* decisions, there would be an argument that claims to partial DNA sequences whose only disclosed utility is for further research -- gene mapping or probing to isolate a full-length sequence whose function is unknown -- are unpatentable.

### 3. Invention

*Is an EST or SNP an "invention" at all?*

#### Answer

Patentable subject matter in the United States is defined by §101 of the patent statute:

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.

It is not the sequence per se of an EST or SNP that constitutes patentable subject matter under this section, but a composition of matter (e.g., a DNA molecule), process or manufacture that is characterized by the sequence.

Moreover, as the above-quoted statutory language indicates, patentability resides both in inventions and discoveries. The fact that the claimed subject matter is based on the discovery of a natural phenomenon does not disqualify it from patent protection, so long as the claims do not read on the product of nature. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

### 4. Novelty

*C. Do ESTs, SNPs or genomes form part of the state of the art in relation to full-length gene sequences?*

## Answer

In the United States, a previously published EST, SNP or genomic DNA sequence would be considered prior art (part of the state of the art) with respect to a claim to a later discovered full-length gene. As discussed below, publication of an EST or SNP would not anticipate a claim to a full-length gene sequence, but could, under certain circumstances, render it obvious.

*D. If it is possible to patent an EST or SNP, should a later, longer gene sequence including that EST or SNP nevertheless be regarded as novel?*

## Answer

In the context of priority of invention, the Court of Appeals for the Federal Circuit has held that conception of a full-length gene does not occur until the inventor can describe the gene "by structure, formula, chemical name, or physical properties." *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993); *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1212-14 (Fed. Cir.) *cert. denied*, 502 U.S. 856 (1991). Based on this same rationale, the prior disclosure of an EST or SNP would not anticipate (destroy novelty) of a later discovered full-length gene that comprises the sequence of the EST or SNP. To anticipate a patent claim, the prior art must disclose each limitation of the claim in the same manner as set forth in the claim. *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996). Because a claim to a full-length gene would contain limitations (sequences) not disclosed by the previously published EST or SNP, it would not be anticipated.

## 5. Obviousness

*A. What standard of obviousness should apply to inventions concerning ESTs, SNPs and genomes?*

## Answer

In the United States, the standards for obviousness for biotechnological inventions are not different from those established for inventions in other fields. ESTs, SNPs and genomic DNA are chemical compounds. The Court of Appeals for the Federal Circuit has held that with respect to claims to DNA, as with claims to other chemical compounds, unpatentability requires that the teachings of the prior art suggest the claimed compound to a person of ordinary skill in the art. *In re Deuel*, 51 F.3d 1552, 1557 (Fed. Cir. 1995). Where the prior art discloses structurally related compounds, obviousness requires that there must be a suggestion of making the specific molecular modifications necessary to achieve the claimed invention. *Id.* at 1558, citing, *In re Jones*, 958 F.2d 347, 351 (Fed. Cir. 1992).

The Federal Circuit has rejected the contention that the availability of a method for isolating DNA renders a claim to a specific DNA molecule obvious. *In re Deuel*, 51 F.3d at 1559; *In re Bell*, 991 F.2d 781, 785 (Fed. Cir. 1993).

These principles suggest that an EST, an SNP or genomic DNA would not be considered obvious absent a suggestion in the prior art of the specific sequences being claimed. The fact that the methods for generating and sequencing ESTs and SNPs are known is irrelevant to the patentability of the specific DNA molecules. Moreover, the fact that it is obvious to try to create these molecules does not render them obvious. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988).

*B. What particular difficulties do courts and patent examiners face in assessing inventive step?*

## Answer

Comparing sequences of claimed DNA to those in the prior art to ascertain whether identical or structurally similar molecules are already known can be a daunting task. High speed computers and large sequence databases must be available to examiners. These tasks have been facilitated in the U.S. by the requirements that patent applicants submit nucleic acid sequences in standardized machine readable format and to limit applications to no more than ten unrelated sequences.

## 6. Sufficiency

*What should be the sufficiency requirements for patents for ESTs, SNPs and genomic DNA?*

### Answer

In the United States, sufficiency of disclosure includes three requirements: a written description of the claimed invention, an enabling disclosure and disclosure of the best mode contemplated by the inventor at the time of filing. 35 U.S.C. § 112. The written description and enablement requirements are separate and distinct. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). Written description issues are discussed in the following section.

Inventions relating to ESTs can present unique disclosure issues, depending on the claim scope sought by the applicant. A disclosure supporting a claim to a specific DNA molecule (*i.e.*, "a DNA molecule consisting of SEQ ID NO. 1") is straightforward. An enabling disclosure requires little more than a listing of the sequence, because such molecules can be synthesized chemically using known techniques.

However, often the patent applicant attempts to obtain broader claims that cover not only the EST or SNP, but also longer molecules, including the full-length gene, that contain the EST or SNP sequence. Examples of such claims include: "a nucleic acid comprising SEQ ID NO. 1" or "a nucleic acid to which a DNA having the sequence of SEQ ID NO. 1 will hybridize under stringent conditions." Claims of this scope present difficult enablement issues, because they presumably would encompass a longer DNA molecule, including a full-length gene whose structure and function are unknown at the time of filing.

Enablement requires that a person of ordinary skill in the art be capable of following the teachings of the specification to practice the claimed invention without engaging in undue experimentation. *In re Wands*, 858 F.2d 731, 736 (Fed. Cir. 1988). The enabling teaching provided by the specification must be commensurate in scope with the claims. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991).

It is questionable whether an inventor who discovers an EST or SNP, without knowledge of the gene from which it is derived or the tissue in which such gene is normally expressed can provide an enabling description of the full-length gene. As discussed below, a further problem is whether an inventor of an EST or SNP can satisfy the written description requirement with respect to claims that encompass the full-length gene.

## 7. Documenting DNA Inventions

*Are there, and should there be special provisions for the written description or claims (e.g., considering unity of invention) of ESTs, SNPs and genomes?*

### Answer

In the United States, the patent applicant must describe the claimed invention in sufficient detail that a person skilled in the art "can clearly conclude that 'the inventor invented the claimed invention [as of the filing date].'" *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997), *quoting Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997). "An adequate written description of a DNA . . . 'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." *Id.*, *quoting Fiers v. Revel*, 984 F.2d at 1171. The *Eli Lilly* case involved a claim to DNA encoding recombinant human insulin. The specification described the cloning of the rat insulin gene and contained a prophetic example describing a general method for obtaining the cDNA encoding human insulin. The court held that the claims to human insulin DNA were invalid for failure of compliance with the written description requirement. The court found that, as of the filing date, the applicant was unable to describe the structure, formula or properties of the human insulin gene sufficiently to ensure that it had been invented.

The court had applied a similar rationale in the context of conception in the *Fiers v. Revel* case. In that case, the court held that possession of a partial sequence of an interferon gene and a general method for obtaining the full-length cDNA was not sufficient to constitute conception of the full-length gene.

This precedent suggests that a claim that encompasses a full-length gene based on disclosure of only an EST or SNP would be unpatentable because of lack of sufficient written description. Unless the applicant can describe the full-length gene by structure, formula or distinguishing characteristics, then the claim scope should be limited to the particular DNA molecules that have been isolated.

## 8. Scope of Protection

*A. Should patent claims for ESTs, SNPs and genomic DNA afford the same protection as other patent claims?*

### Answer

If the patent offices and courts are diligent in limiting the scope of claims to what is supported by the disclosure, there should be no reason for treating claims to ESTs, SNPs and genomic DNA any differently than claims to inventions in other fields. For example, if a claim to an EST is limited to a DNA molecule "consisting of" the disclosed sequence, then later researchers who discover a full-length gene containing the sequence of that EST will only infringe if they use the claimed EST to isolate the full-length gene.

Accordingly, it is not necessary or desirable that special infringement rules or compulsory licensing be applied to claims in this field. Compulsory licensing has long been disfavored in the United States. U.S. courts do have the authority to consider the public interest in deciding whether to issue an injunction against patent infringement; however, an injunction usually will issue once there is a finding that the asserted patent is infringed and has not been proven to be invalid or unenforceable.

The United States does recognize a limited experimental use exemption. Uses "for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry" may be exempt from infringement, but uses having "definite, cognizable, and not insubstantial commercial purposes" are infringing. *Roche Products v. Bolar Pharmaceutical Co.*, 733 F.2d 858, 863 (Fed. Cir. 1984).

An issue that remains unclear has to do with the measure of damages in the event that a patented DNA molecule is used in a commercial research program which results in a valuable non-infringing product. For example, if a patented EST is used for isolating a full-length gene that subsequently is used to develop a pharmaceutical product, is the holder of the EST patent entitled to damages in the form of a royalty based on the sale of the pharmaceutical product? The patent statute simply provides that the patentee is entitled to damages sufficient to compensate for the infringement, which shall in no event be less than a reasonable royalty. 35 U.S.C. § 285. Courts are entitled to consider a wide range of factors in determining what is a reasonable royalty, including existing licensing practices. *Georgia-Pacific Corp. v. U.S. Plywood-Champion Papers, Inc.*, 318 F. Supp. 1116, 1120 (S.D.N.Y. 1970).

*B. If the answer to (a) is "no" could there be restrictions on the scope of protection of such patents, e.g.;*

*(i) restriction to the known use of the gene (or fragment);*

*(i) compulsory licensing by the patentee so as to make research tools available for further inventions.*

### Answer

As discussed above, it is not seen that special infringement rules or compulsory licensing requirements are necessary or appropriate for inventions in this field. The safeguard against broad patent claims that unfairly interfere with subsequent research is for patent offices and courts to ensure that patent claims are limited to a scope that is supported by the patent disclosure.