UNC SCHOOL OF LAW

NORTH CAROLINA JOURNAL OF LAW & TECHNOLOGY

Volume 6
Issue 1 *Fall 2004*

Article 4

10-1-2004

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Amy Nelson[1]

I. Introduction

Obviousness, or inventive step, has been called the ultimate bar to patentability.[2] The purpose of the nonobviousness requirement is to complement the novelty requirement and to extend the scope of the relevant prior art beyond anticipatory prior art.[3] This ensures that an invention constitutes a sufficient advance in technology to warrant an exclusive right. Adoption of an obviousness standard is a balancing act that requires weighing the inventor's right to exclude and the public's need to gain useful technological knowledge in exchange for that patent right. As a consequence of its interpretive flexibility, the application of obviousness has varied greatly among nations. This is particularly true for its application to nucleic acid molecules.

The Agreement on Trade-Related Intellectual Property Rights ("TRIPS") has attempted to bring some international uniformity to the application of obviousness or inventive step rules.[4] TRIPS Article 27(1) provides that "patents shall be

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[2] Lee Petherbridge, *Intelligent TRIPS Implementation: A Strategy for Countries on the Cusp of Development*, 22 U. PA. J. INT'L ECON. L. 1029, 1053 (2001).

[3] *Id.*

[4] Agreement on Trade-Related Aspects of Intellectual Property Rights, April 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, LEGAL INSTRUMENTS—RESULTS OF THE URUGUAY ROUND vol. 31, 33 I.L.M. 81 (1994), *available at*

available for any inventions, whether products or processes, in all fields of technology, provided they are new, involve an inventive step and are capable of industrial application."[5] Exclusive patent rights are available for all products regardless of their status as an import or a domestic creation.[6] The TRIPS Agreement has been ratified by 120 countries.[7] TRIPS is an integral part of the WTO Agreement, and a country cannot be a member of the World Trade Organization ("WTO") without being a party to the TRIPS Agreement.[8] As a signatory of TRIPS, the United States agreed to ensure that its obviousness requirement meets the standards of the 1994 Agreement.[9] The European Patent Office's inventive step requirement is also governed by the TRIPS Agreement.[10] Japan has both signed and ratified the TRIPS Agreement.[11] Australia is also bound by the TRIPS Agreement.[12]

TRIPS, however, only sets the minimum patentability standards with which signatories must comply.[13] National patentability rules may vary beyond the minimum, and member states are free to set their own intellectual property laws. To the extent that different countries have differing patentability standards, those differences in national laws may be significant.

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http://www.wto.org/english/tratop_e/trips_e/t_agm3_e.htm (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology) [hereinafter TRIPS].

[5] *Id.* at art. 27(1).

[6] *See* S.K. Verma, *TRIPS—Development and Transfer of Technology*, 27 IIC: INT. REV. INDUS. PROP. & COPYRIGHT L. 331, 343 (1996).

[7] Charles Lawson, *Patenting Genetic Materials: Old Rules May Be Restricting the Exploitation of a New Technology*, 6 J.L. & MED. 373, 384 n.109 (1999).

[8] Verma, *supra* note 6, at 331–32.

[9] *See* Katsuya Saito & Rosemary Sweeney, *Assessment of Inventive Step or Obviousness in the United States, Europe, and Japan* 1, *at* http://www.law.washington.edu/casrip/harmonization/PDF/obviousness.pdf (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).

[10] *Id.* at 3.

[11] Eiji Katayama, *The Need and Possible Means of Implementing the Convention on Biodiversity into Patent Laws*, 26 A.I.P.P.I. 44, 45 (2001).

[12] Lawson, *supra* note 7, at 384.

[13] *See id.* at 374–75.

As a result, TRIPS allows for differing standards of inventive step or obviousness under different national laws.

In recent years, there has been an explosion of patent applications in biotechnology, particularly applications directed to nucleic acid molecules. TRIPS countries, however, have adopted a variety of standards for determining obviousness or inventive step for nucleic acid molecules. Part II discusses legal standards as applied in the United States, Australia, Europe, and Japan, with particular emphasis on the distinctions between U.S. laws and those of other countries. Part III discusses the implications of having different legal standards in different countries.

II. Standards for Determining Obviousness or Inventive Step of Nucleic Acid Molecules

A. United States

1. Statutory Law

Determination of obviousness in the United States is governed by Section 103 of the Patent Act of 1952, which recites that:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which such subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.[14]

[14] 35 U.S.C. § 103(a) (2000).

2. Relevant Prior Art

In the United States, the prior art that is applied must be from an analogous field, and the number of references that are applied is not limited.[15] The prior art that can be applied includes "secret art," i.e. pending patent applications.[16] The prior art refers to everything that is known, published and available to the public in the past.[17] Oral disclosures are only considered if they occurred within the boundaries of the United States.[18] The United States provides a grace period that permits publication of the invention by the inventor up to one year prior to filing of the patent application.[19]

3. Prima Facie Test

Application of Section 103 was clarified in a seminal decision:

> Under § 103, the scope and content of the prior art and the claims at issue are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.[20]

One of the earliest court decisions regarding obviousness as it applies to nucleic acid molecules in the United States related to isolation of a human genomic DNA encoding erythropoietin ("EPO").[21] The prior art taught an isolated monkey cDNA encoding EPO.[22] The United States Court of Appeals for the

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[15] Saito & Sweeney, *supra* note 9, at 2.
[16] *Id.*
[17] Akim F. Czmus, *Biotechnology Protection in Japan, the European Community, and the United States*, 8 TEMP. INT'L & COMP. L. J. 435, 439 (1994).
[18] *See id.* at 459.
[19] *See id.*
[20] Graham v. John Deere Co., 383 U.S. 1, 17 (1966).
[21] Amgen Inc. v. Chugai Pharm. Co. Ltd., 927 F.2d 1200 (Fed. Cir. 1991).
[22] *See id.* at 1208.

Federal Circuit (hereinafter Federal Circuit) held that while it might have been obvious to try to isolate the human genomic clone using the monkey cDNA as a probe, it was not obvious to succeed in isolating the human EPO gene.[23] There was no reasonable expectation of success given the high degree of degeneracy of the probe that was required for ultimate success.[24] Hence, the court focused on the likelihood that the method of DNA isolation would succeed.

In stark contrast to the *Amgen* decision, more recent decisions by the Federal Circuit have focused on the structural obviousness of the nucleic acid molecules themselves, rather than on the obviousness of the methods for their isolation. In *In re Bell*,[25] the prior art disclosed amino acid sequences for insulin-like growth factor ("IGF") polypeptides, as well as general methods for cloning genes.[26] The court held that the claimed invention, directed to specific nucleic acid molecules that encode human IGF, was non-obvious because there are a vast number of nucleic acid molecules that could encode the prior art proteins, and the prior art failed to suggest which of the possible sequences was the human nucleic acid molecule.[27]

The landmark decision *In re Deuel*[28] has set the stage for obviousness with respect to nucleic acids in recent years. The claimed invention was directed to an isolated nucleic acid molecule encoding heparin-binding growth factors ("HBGF"), proteins found in urine and placental tissue that stimulate cell division and replacement of damaged or diseased tissue.[29] The prior art disclosed the first 19 amino acids of heparin-binding brain mitogens ("HBBM"), proteins found in the brain that are identical for human and bovine, and the prior art also taught general methods of DNA isolation.[30] The Federal Circuit held that whereas structural relationships may provide the motivation to

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[23] *Id.* at 1208–09.
[24] *See id.*
[25] 991 F.2d 781 (Fed. Cir. 1993).
[26] *Id.* at 783.
[27] *Id.* at 784.
[28] 51 F.3d 1552 (Fed. Cir. 1995).
[29] *See id.* at 1554–55.
[30] *See id.* at 1556.

obtain new compounds by modifying prior art compounds, here, the prior art taught only proteins, not closely related DNA molecules.[31] In view of the degeneracy of the genetic code, and hence the multitude of DNA molecules that may encode any given protein, knowledge of the protein does not render obvious a particular DNA encoding it.[32] Further, the Court clearly articulated that prior art methods for isolating DNA molecules are "irrelevant" to the obviousness test for DNA molecules thereby obtained.[33]

The import of the decisions in *Bell* and in *Deuel* in the United States is that a DNA molecule will be determined to be obvious only if it is structurally similar to prior art products, even if one of skill in the art would consider it obvious to obtain the DNA molecule using familiar prior art methods. The Federal Circuit has focused on the obviousness of the nucleic acid sequence itself rather than on the obviousness of the method of isolating the nucleic acid sequence.[34] A DNA molecule is non-obvious and patentable because its sequence could not have been predicted without isolation and sequencing of the DNA molecule.[35] The prior disclosure of the amino acid sequence does not render the DNA sequence obvious due to the degeneracy of the genetic code.[36] Prior art methods for isolating and sequencing DNA are irrelevant.[37] As a consequence of the Federal Circuit decisions, the United States Patent and Trademark Office ("PTO") has a relatively low threshold for obviousness in the patenting of nucleic acid molecules as compared to most other countries.

Interestingly, after the *Bell* decision the Board of Patent Appeals and Interferences held that recombinant DNA molecules encoding swine growth hormone were obvious.[38] In *Ex parte Movva*, the prior art taught the partial amino acid sequence of

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[31] *See id.* at 1558.
[32] *Id.* at 1558–59.
[33] *Id.* at 1559.
[34] *See* David Keays, *Patenting DNA and Amino Acid Sequences—An Australian Perspective*, 7 HEALTH L.J. 69, 83 (1999).
[35] *See id.*
[36] *See id.*
[37] *See id.*
[38] *Ex parte* Movva, 31 U.S.P.Q.2d 1027 (1993).

swine growth hormone polypeptide, the high degree of sequence relatedness between swine, bovine and human growth hormone polypeptides, as well as isolated DNA molecules encoding human and bovine growth hormone.[39] The Board held that based on the prior art, it would have been obvious to one of ordinary skill in the art to isolate a DNA molecule encoding swine growth hormone using probes based on the partial amino acid sequence.[40] The Board distinguished the case from *Bell* because the record did not show that a large number of nucleic acids could encode the polypeptide as in *Bell* and because multiple DNA sequences encoding growth hormone polypeptides from different species were disclosed in the prior art unlike in *Bell*.[41]

Shortly after the *Deuel* decision, the Board of Patent Appeals and Interferences held that a cDNA encoding brain beta-amyloid polypeptide associated with Alzheimer's disease was obvious.[42] The prior art taught a polypeptide isolated from cerebrovascular amyloid deposits of Alzheimer's patients and provided guidelines for synthesis of degenerate oligonucleotide probes.[43] The prior art also taught methods for constructing and screening cDNA libraries.[44] The Board held that it would have been obvious based on the prior art to isolate a cDNA encoding brain beta-amyloid polypeptide from an adult brain cDNA library.[45] The Board reasoned that here, unlike in *Bell* or *Deuel*, there is something in the prior art that leads to isolation of the claimed DNA.[46] Further, the Board noted that there is nothing intrinsically wrong with considering methodology in an obviousness analysis, depending on the logic of the rejection.[47]

In contrast, the Board found that there was no interference in fact between two nucleic acid sequences with only minor

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[39] *See id.* at 1029.
[40] *See id.* at 1032.
[41] *See id.* at 1033.
[42] *Ex parte* Goldgaber, 41 U.S.P.Q.2d 1172 (Bd. Pat. App. & Int. 1995).
[43] *Id.* at 1173–74.
[44] *Id.* at 1174.
[45] *Id.*
[46] *Id.* at 1176.
[47] *Id.*

differences.[48] Lilly disclosed a cDNA encoding human protein C, and The University of Washington ("UW") disclosed a DNA sequence that differed at two nucleotides.[49] The Board held that Lilly's nucleic acid sequence, taken with the prior art, would not have suggested the nucleic acid sequence of UW, and further that the amino acid sequence of protein C would not have suggested to one of skill in the art the UW nucleic acid sequence.[50] Therefore, the Lilly nucleic acid sequence and the UW nucleic acid sequence were patentably distinct, and there was no interference in fact.[51] The Federal Circuit affirmed the Board's decision.[52]

Although *Deuel* is still the law of the land in the United States, it appears that the Board of Appeals and Interferences may still occasionally find fact patterns that can be distinguished from *Deuel*, wherein obviousness is applicable to nucleic acid molecules. It may be that the Federal Circuit has a more pro-patent approach to obviousness with respect to biotechnology than the PTO.[53] The decision in *Deuel* was perhaps the result of an increasing tension between the statutory requirements of patentability, specifically obviousness, and pressure from the biotechnology industry that patent protection of DNA molecules is necessary.[54]

4. Secondary Criteria

In the United States, secondary considerations "might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented."[55] Secondary considerations are an essential component of the obviousness determination and must always be considered if offered by the

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[48] Bd. of Regents v. Eli Lilly & Co., 2002 Pat. App. LEXIS 176 (Bd. Pat. App. & Int. 2002).
[49] *See id.* at *4, *8.
[50] *Id.* at *12–13, *43–44.
[51] *Id.* at *44, *48.
[52] Eli Lilly & Co. v. Bd. of Regents, 334 F.3d 1264 (Fed. Cir. 2003).
[53] *See* Phillipe Ducor, *Recombinant Products and Nonobviousness: A Typology*, 13 SANTA CLARA COMPUTER & HIGH TECH. L. J. 1, 42 (1997).
[54] *See id.* at 42–43.
[55] Graham v. John Deere Co., 383 U.S. 1, 17–18 (1966).

applicant.[56] They may include failure of others, long felt but unsolved need, unexpected results or unexpected properties, commercial success, copying, licensing, and skepticism of skilled artisans before the invention.[57]

Secondary considerations have played a role in obviousness determinations for nucleic acid molecules. For example, in *Bell* the court found that whereas the prior art taught that probes should be greater than fourteen to sixteen nucleotides only if four to five codons are non-degenerate, Bell used a twenty-three nucleotide probe that was degenerate at every codon.[58] The court clearly considered the unexpected results of the probes employed by Bell, the teaching away of the prior art, and the skepticism of those of skill in the art prior to the invention in its obviousness analysis, and deemed the invention of Bell to be non-obvious based at least in part on these secondary considerations.[59]

One commentator has argued that although DNA is a chemical compound, it is more importantly a carrier of information.[60] The Federal Circuit, therefore, has failed to adjust existing paradigms for obviousness to the DNA technology.[61] Consideration of only structural similarity for DNA molecules, as for chemical molecules, fails to recognize that DNA molecules are informational molecules.[62] This essentially eliminates the requirement of obviousness, even when all the necessary information is available in the prior art to identify the DNA molecules.[63] Second generation DNA and protein molecules often lack the unexpected properties that are typically required to overcome an obviousness rejection based on secondary criteria.[64]

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[56] Saito & Sweeney, *supra* note 9, at 2–3.
[57] *In re* Rouffet, 149 F.3d 1350, 1355 (3rd Cir. 1998).
[58] *In re* Bell, 991 F.2d 781, 784 (2nd Cir. 1993).
[59] *Id.* at 785.
[60] Arti K. Rai, *Intellectual Property Rights in Biotechnology: Addressing New Technology*, 34 WAKE FOREST L. REV. 827, 836 (1999).
[61] *Id.*
[62] Ducor, *supra* note 53, at 44.
[63] *Id.* at 45.
[64] *Id.* at 50.

B. Australia

1. Statutory Law

Inventive step is governed by section 7(2) of the 1990 Patents Act in Australia that provides:

> For the purposes of this Act, an invention is to be taken to involve an inventive step when compared with the prior art base unless the invention would have been obvious to a person skilled in the relevant art in the light of the common general knowledge as it existed in the patent area before the priority date of the relevant claim, whether that knowledge is considered separately or together with either of the kinds of information mentioned in subsection (3), each of which must be considered separately.[65]

2. Relevant Prior Art

In Australia, prior art may be any information made available in a document or in a public act,[66] hence public use or oral disclosures may satisfy the prior art requirement. Australia, like the United States, has geographical limitations on the prior art that can be used, so oral disclosures may be limited to those in Australia.[67] Relevant prior art may also include, as in the United States, information in a specification with a priority date earlier than the claimed invention.[68]

Prior to 1990, the common general knowledge which was considered for inventive step determinations was limited to knowledge within Australia.[69] However, since the 1990 Act, the

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[65] Patents Act, 1990, § 7(2) (Austl.).

[66] *Id.* § 7(3), at 301.

[67] Margo A. Bagley, *Patently Unconstitutional: The Geographical Limitation on Prior Art in a Small World*, 87 MINN. L. REV. 679, 688 n.38 (2003).

[68] *See* Patents Act, 1990, Sched. 1, at 393 (defining "prior art base").

[69] *See e.g.*, Kirin-Amgen Inc. v. Univ. of Wash. (1996) 33 I.P.R. 557, 563 (Austl.), *available at* http://www.austlii.edu.au/cgi-bin/disp.pl/au/cases/cth/APO/1995/61.html (last visited Nov. 16, 2004) (on file with the North Carolina Journal of Law & Technology).

common general knowledge is not so restricted and need only relate to the area of the patented invention.[70]

3. Prima Facie Test

The basic rule that is applied in an obviousness analysis is set forth in *Wellcome Foundation Ltd. v. VR Lab.*:

> [T]he question of obviousness involves asking the question whether the invention would have been obvious to a non-inventive worker in the field, equipped with the common general knowledge in that particular field as at the priority date, without regard to documents in existence but not prior art of such common general knowledge.[71]

The court clarifies, "[t]he test is whether the hypothetical addressee faced with the same problem would have taken as a matter of routine whatever steps might have led from the prior art to the invention, whether they be the steps of the inventor or not."[72] The use of such a problem solving approach necessarily carries with it the inherent danger of hindsight reasoning. Because one knows the invention when performing the analysis, it is easy to find the invention to be an obvious way to solve the problem.

To establish an inventive step with respect to nucleic acid sequences, a similar question is generally asked, "[w]as it, for practical purposes, obvious to a person skilled in the particular art, armed with all the common knowledge of his or her art, that he or she could do what the patent proposes?"[73] Typically, for nucleic acid sequences, there need only be a scintilla of invention, so the inventive step requirement is easily satisfied in most instances.[74] In fact, the inventive step requirement has not been a major

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[70] Patents Act, 1990, § 7(2), at 301.

[71] Wellcome Found. Ltd. v. VR Lab. (Aust.) Pty. Ltd. (1984) 34 A.L.R. 213, 216 (Austl.), *available at* http://www.austlii.edu.au/au/cases/cth/high_ct/148clr262.html (last visited Nov. 16, 2004) (on file with the North Carolina Journal of Law & Technology).

[72] *Id.* at 228.

[73] Keays, *supra* note 34, at 79.

[74] *Id.*

obstacle to patenting DNA or amino acid sequences in Australia.[75] This may well be due to the use of hindsight resulting from the problem solving test employed in Australia.

Although there has been no consideration by Australian courts of the inventive step requirement for nucleic acid molecules, the Deputy Commissioner of Patents has considered the issue in a number of opposition proceedings.[76] One of the earliest decisions by the Australian Patent Office regarding nucleic acid molecules was *Genentech Inc. v. Celtrix Pharmaceuticals Inc.*[77] The invention was directed to an isolated DNA molecule encoding the insulin-like growth factor binding protein, BP53, and methods for recombinant production of therapeutically significant quantities of the protein.[78] The Patent Office reasoned that the patent holder provided evidence that only when hybridizations were done with three specific pools of probes under low stringency conditions was the BP53 DNA molecule identified, and there was no teaching or suggestion in the prior art of using such a probing strategy involving pools of mixed probes.[79] The opposition provided no evidence of a person working in the field using methods of common knowledge in the art to isolate a BP53 DNA.[80] There were difficulties that had to be overcome in a non-routine inventive manner to isolate the BP53 DNA molecule, and therefore there was an inventive step.[81]

Similarly, the Patent Office found a claimed invention directed to a recombinant non-glycosylated human interleukin-2 patentable over the natural interleukin-2 which is a glycosylated

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[75] *Id.* at 80.

[76] Dianne Nicol & Jane Nielsen, *The Australian Medical Biotechnology Industry and Access to Intellectual Property: Issues for Patent Law Development*, 23 SYDNEY L. REV. 347, 365 (2001).

[77] (1993) 26 I.P.R. 629 (Austl.), *available at* http://www.austlii.edu.au/au/cases/cth/APO/1993/39.html (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).

[78] *Id.* at 6–7.

[79] *Id.* at 6–7.

[80] *Id.* at 6.

[81] *Id.* at 7.

protein produced by T cells.[82] The Patent Office held that the opposition had not shown that a particular method for purifying non-glycosylated human recombinant interleukin-2 would have been obvious from known techniques, and hence the opposition had failed to demonstrate the lack of an inventive step.[83]

More recently, there was an opposition proceeding in Australia relating to serotonin, or 5-hydroxytryptamine ("5-HT"), a neurotransmitter that interacts with proteins of the 5-HT receptor family.[84] The claimed invention was directed to isolated genes from the human 5-HT_{1D} receptor sub-family, isolated by probing a human cDNA library with a dog clone, RDC4.[85] The closest prior art reference taught isolation of cDNA clones from dog, including RCC4, using probes based on a family of G protein-coupled receptors including the 5-HT_{1A} receptor.[86] The prior art reference further proposed that the clone could be a member of the large family of serotonin receptors but stated that functional and binding studies will be required to confirm its function.[87] The Australian Patent Office held that without further characterization of the RDC4 clone, the skilled worker would not have recognized its importance and would not have used the clone to isolate the human 5-HT_{1D} receptor gene.[88] RDC4 was an orphan clone whose function was unknown, and one of skill in the art would not have probed a human library with a gene that was only partly characterized.[89] The Patent Office found, therefore, that the opposition had not established a lack of inventive step.[90]

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[82] Takeda Chem. Indus. v. Hoffman-La Roche Akteingesellschaft (1996) A.P.O. 3 (Austl.), *available at* http://www.austlii.edu.au/au/cases/cth/APO/1996/3.html (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).

[83] *Id.* at 7.

[84] Synapic Pharm. Corp. v. Astra Aktiebolag (1998) 43 I.P.R. 461 (Austl.), *available at* http://www.austlii.edu.au/cgi-bin/disp.pl/au/cases/cth/APO/1998/49.html (last visited Nov. 12, 2004) (on file with the North Carolina Journal of Law & Technology).

[85] *Id.* at 462–63.

[86] *Id.* at 472.

[87] *Id.*

[88] *Id.* at 473.

[89] *Id.* at 472–73.

[90] *Id.* at 473.

In sum, the Australian Patent Office has made its inventive step determinations based on the obviousness of methods of isolation of the nucleic acid molecules and not based on the structural obviousness of the nucleic acid molecules themselves, as has been the basis for obviousness analysis in the United States.

4. Secondary Criteria

Secondary, or objective, criteria are sometimes relied upon for obviousness determinations in Australia. For example, in *Kirin-Amgen Inc. v. University of Washington*[91] the claimed invention was directed to an isolated DNA encoding erythropoietin, as well as DNAs that hybridize to said DNA under stringent conditions. The Australian Patent Office held that the amino acid sequence of erythropoietin was not known in Australia with sufficient accuracy to allow identification of the gene, and therefore the DNA was not obvious.[92] Furthermore, isolation of the DNA was non-obvious as evidenced by the large amount of time, money, and effort that was expended by several parties to clone the gene without success.[93] In essence, the Deputy Commissioner of Patents found that isolating the erythropoietin gene involved an inventive step because the cloned gene was artificially created, and in view of secondary criteria.

This decision suggests that obviousness analysis in Australia has become almost conflated with anticipation. Patents on nucleic acid sequences have been granted with almost no evidence other than the failure of the prior art to disclose the sequence.[94] This approach fails to acknowledge the widespread recognition of the genetic dogma—that there is a gene that codes for every protein—and that cloning the gene encoding a newly isolated protein is the obvious next step for a person skilled in the

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[91] Kirin-Amgen Inc. v. Univ. of Wash. (1996) 33 I.P.R. 557 (Austl.), *available at* http://www.austlii.edu.au/cgi-bin/disp.pl/au/cases/cth/APO/1995/61.html (last visited Nov. 11, 2004) (on file with the North Carolina Journal of Law & Technology).

[92] *Id.* at 565.

[93] *Id.* at 564.

[94] Lawson, *supra* note 7, at 379.

art of molecular biology.[95] Many have criticized the decisions by the Australian Patent Office for setting too low a threshold for obviousness, i.e. for putting too much value on the first to sequence.[96] IP Australia has routinely allowed patents on genes with no evidence other than the sequence, thereby failing to recognize the routine nature of cloning genes.[97] In addition, broad claims are often granted by IP Australia to encompass genes encoding functional derivatives or parts of the enzyme, or genes with a percentage of similarity with the disclosed nucleic acid sequence, or that hybridize under low stringency with the disclosed nucleic acid sequence, or to genes that encode a modified enzyme having multiple amino acid substitutions, deletions or alterations.[98]

C. Europe

1. Statutory Law

Inventive Step is determined in Europe according to Article 56 of the European Patent Convention which states, "An invention shall be considered as involving an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art."[99]

2. Relevant Prior Art

Unpublished patent applications cannot serve as prior art in Europe.[100] Furthermore, Europe does not have a grace period allowing inventors to publish prior to filing for a patent.[101] In Europe, prior art includes oral disclosures from anywhere in the

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[95] *Id.*
[96] Nicol & Nielsen, *supra* note 76, at 365.
[97] Lawson, *supra* note 7, at 379.
[98] *Id.* at 380–81.
[99] European Patent Convention, art. 56, *in* VOLKER VOSSIUS ET AL., EUROPEAN MATERIALS AND INDEX 27 (1995), *available at* http://www.european-patent-office.org/legl/epc/e/contents.html (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).
[100] Saito & Sweeney, *supra* note 9, at 4.
[101] Czmus, *supra* note 17, at 459.

world.[102] The use of more than a single secondary reference is typically considered to be beyond obviousness in Europe.[103]

3. Prima Facie Test

The basic approach to an obviousness determination in Europe generally involves three steps: (1) the closest prior art is determined; (2) the technical problem is determined by comparing the results achieved in the invention with the closest prior art; and (3) the obviousness of the solution is assessed in light of other art and the knowledge of a person with ordinary skill in the art.[104]

Even though hindsight is forbidden, determining the technical problem solved by the invention necessarily involves hindsight.[105] The basic rule in Europe is that a prima facie case of obviousness is shown if a person of ordinary skill in the art would (not could) have made the invention.[106] Unlike in the United States, a person of ordinary skill in the art can be a team of experts.[107]

One of the earliest court decisions in Europe regarding inventive step as it applies to nucleic acid molecules involved an invention directed to isolated DNA molecules encoding human tissue plasminogen activator ("t-PA").[108] In that case, the court held that it was obvious to the person skilled in the art to produce human t-PA by recombinant DNA technology.[109] Oligonucleotide probing was a known technique, and the skilled worker would have arrived at the claimed invention because the choice of oligonucleotide probes did not require skill and experience of a high order.[110] In fact, all the teams that set out to produce human t-PA by recombinant DNA technology succeeded.[111] The court

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[102] *Id.*
[103] Saito & Sweeney, *supra* note 9, at 4.
[104] *Id.*
[105] *Id.*
[106] *Id.* at 5.
[107] *Id.* at 4.
[108] *Genentech Inc.'s Patent*, [1989] R.P.C. 147 (Eng. C. A. 1988).
[109] *Id.* at 243.
[110] *Id.* at 277, 282–83.
[111] *Id.* at 244.

reasoned that the monopoly that would be granted to the inventors by a patent far outstrips any legitimate reward for their success in winning the race to recombinant expression of the gene, and hence the claimed invention failed for want of an inventive step.[112] In the decision, the Court focused on the obviousness of the methods of isolating the DNA molecules, rather than on the structural obviousness of the DNA molecules as in the United States, and the court was greatly concerned about giving away patent rights based on the speed of performing the methods rather than based on ingenuity.

The Technical Board of Appeals' review of cases relating to nucleic acid molecules, has found an inventive step when there is evidence of particular difficulties in the isolation procedures. For example, the Board considered claims to a DNA comprising a coding sequence for the precursor to human IL-1.[113] Although the prior art disclosed cloning of a murine IL-1 cDNA, the prior art also disclosed significant differences between human and murine IL-1.[114] Hence, the Board held that the skilled person would not have had a reasonable expectation that the human and murine DNAs were so homologous that one could be used to probe for the other, and therefore the cloning of human IL-1 DNA was inventive.[115]

The lack of availability of suitable probes was the basis for the Board finding an inventive step for an invention directed to a DNA molecule encoding the insulin-like growth factor binding protein, BP53.[116] The prior art disclosed SDS-PAGE electrophoresis of BP53 and sequencing of fifteen amino acids at

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[112] *Id.* at 247, 260.

[113] Dainippon Pharm. Co. Ltd. v. Otsuka Pharm. Co. Ltd., Eur. Pat. Off., T 236/96 (1999), *available at* http://legal.european-patent-office.org/dg3/biblio/t960236eu1.htm (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).

[114] *Id.* at 18.

[115] *Id.* at 19.

[116] Genentech, Inc. v. Celtrix Pharm., Inc., Eur. Pat. Off., T 637/97 (2000), *available at* http://legal.european-patent-office.org/dg3/biblio/t970637eu1.htm (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).

the amino terminus.[117] The Board held that the skilled person would not have had a good starting point for making suitable probes for screening DNA libraries for a BP53 DNA based on the work on other genes because of the unique characteristics of each gene.[118] The sequence of fifteen amino acids was useless for designing probes due to its high level of degeneracy, and hence the skilled person would not have had a reasonable expectation of success in isolating a DNA molecule encoding BP53.[119] The Board concluded that the claimed invention satisfied the inventive step requirement.[120]

In contrast, the Technical Board of Appeals has failed to find an inventive step when the methods of isolation are routine and predictable. For example, the Board considered claims to DNA molecules encoding preprochymosin as well as its mature form.[121] The prior art disclosed that chymosin is a milk clotting protein that has a precursor protein of 365 amino acids, and the prior art also taught the isolation of a clone comprising 80% of the prochymosin molecule.[122] The Board held that the person skilled in the art would be reasonably confident that based on the prior art and the standard knowledge, one could successfully clone the DNA molecules encoding preprochymosin as well as its mature form. Hence, the Board found that the claimed invention lacked an inventive step.[123]

The Board held similarly when the claimed invention was directed to a DNA molecule encoding human insulin-like growth factor ("IGF") II having a particular sequence.[124] The prior art disclosed proteins belonging to the IGF family and suggested that the amino acid sequences of IGF-I and IGF-II could be used to

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[117] *Id.* at 6–7.
[118] *Id.* at 8–9.
[119] *Id.* at 9.
[120] *Id.* at 11.
[121] Unilever N. V. v. Celltech Ltd. Chr. Hansens Lab. A/S, Eur. Pat. Off., T 386/94 (1996).
[122] *Id.* at 193–94.
[123] *Id.* at 196.
[124] Chiron Corp. v. US Surgical Corp., Eur. Pat. Off., T 475/93 (1997), *available at* http://legal.european-patent-office.org/dg3/biblio/t930475eu1.htm (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).

determine oligonucleotides for use in screening for DNA molecules.[125] The prior art also taught a cDNA library from liver.[126] The Board held that the skilled person would have expected to successfully isolate an IGF-II DNA molecule by probing the liver cDNA library, since the liver was known to be the site of production of IGF-II, and hence the claimed subject matter did not involve an inventive step.[127]

When the prior art taught the isolation of *Bacillus thuringiensis* ("*Bt*") genes from 32 different strains of *Bt* using a *Bt* DNA probe, and taught that *Bacillus thuringiensis* Berliner contains an insecticidal gene, the Board held that claims directed to a DNA molecule comprising the *Bt* gene from *Bt* Berliner lacked an inventive step because the isolation and sequencing of the *Bt* Berliner gene was done by a well-established method, and there was no evidence that any difficulties were encountered.[128]

The Board similarly assessed inventive step with regard to a claimed invention directed to a DNA molecule encoding a mammalian monokine induced by gamma interferon ("MIG") with at least 90% identity to particular nucleic acid sequence.[129] The prior art disclosed an isolated mouse DNA molecule encoding cytokine induced by interferon, which DNA molecule had 78% identity to the particular nucleic acid sequence claimed, and the prior art suggested studying the wide involvement of such macrophage products because of the involvement of macrophages in human health and disease.[130] The Board reasoned that isolation of the human cytokine cDNA was carried out in a straightforward manner using the prior art DNA as a probe, and the skilled person would have considered cloning of the human cDNA as a matter of

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[125] *Id.* at 441.
[126] *Id.* at 443.
[127] *Id.* at 443, 446.
[128] Aventis Crop Sci. v. Agrigenetics LP Novartis AG, Eur. Pat. Off., T 1054/97 (2000), *available at* http://legal.european-patent-office.org/dg3/biblio/t971054eu1.htm (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).
[129] *In re* Farber, Eur. Pat. Off., T 111/00 (2002), *available at* http://legal.european-patent-office.org/dg3/biblio/t000111eu1.htm (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).
[130] *Id.* at 2, 4.

routine experimentation since the probe was available.[131] Hence, as a general rule the Board is unlikely to find an inventive step provided that the starting materials are available and the methods of DNA isolation are routine.

In a decision wherein the closest reference was not technically available as prior art based on an assessment of priority, the Board nonetheless went through an obviousness analysis with respect to the reference.[132] The claimed invention was directed to recombinant DNA encoding the pectin lyase, pelC, having a particular amino acid sequence.[133] Since the reference disclosed a recombinant DNA from *Aspergillus niger* encoding the pectin lyase, pelD, the Board reasoned that the problem to be solved was isolation of a recombinant DNA encoding another pectin lyase from *A niger*.[134] The Board went on to recognize that screening for a gene encoding a protein using a homologous DNA probe was a matter of common knowledge, and hence, it would not have required inventive skills to isolate the pelC gene using the pelD DNA as a probe.[135] Again, when the probe was available and the screening methods were routine, the Board failed to find an inventive step.

In summary, unlike the United States' approach of evaluating the obviousness of nucleic acid molecules based on structural similarity, Europe typically evaluates inventive step based on the obviousness of the methods of isolation of the nucleic acid molecules.

4. Secondary Criteria

Objective indicia of nonobviousness are generally considered to play a very secondary role compared to the technical

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[131] *Id.* at 5–6.
[132] Novartis v. DSM Gist Holding B.V., Eur. Pat. Off., T 479/97 (2001), *available at* http://legal.european-patent-office.org/dg3/biblio/t970479eu1.htm (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).
[133] *Id.* at 1.
[134] *Id.* at 11–12.
[135] *Id.* at 13.

considerations in Europe,[136] however, this is not to say that secondary considerations have not played any role in nonobviousness determinations, especially for nucleic acid molecules. The Technical Board of Appeals at the European Patent Office has noted that an inventive step could be found if a claimed sequence imparts an unexpected property to the nucleic acid molecule.[137] The Board failed to find an inventive step when methods of isolation were routine and the isolated gene did not have any unexpected features.[138]

On at least one occasion, the Board of was willing to find an inventive step when the nucleic acid molecules exhibited improved properties. In *Biogen*,[139] the Board held that claims directed to recombinant DNA molecules comprising specific deposited DNA inserts encoding IFN-alpha satisfied the inventive step requirement.[140] Although the prior art taught recombinant expression in *E. coli* of a polypeptide with human leukocyte interferon activity, and taught the means for fishing for similar DNA molecules by hybridization, the specifically claimed DNA inserts showed some surprising technical effects as compared to the prior art.[141] The claimed DNA inserts were found to serve as a precursor for IFN-alpha2, which was more than 30 times more active than the prior art IFN-alpha1.[142] The structural differences, therefore, conferred a valuable property on the DNA molecules, and the claimed DNA molecules were found to be based on an inventive step.[143] In sum, the secondary consideration of the unexpected property of the DNA inserts and their encoded protein

[136] Saito & Sweeney, *supra* note 9, at 4–5.
[137] *In re* Farber, Eur. Pat. Off., T 111/00 (2002), *available at* http://legal.european-patent-office.org/dg3/biblio/t000111eu1.htm (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).
[138] Aventis Crop Sci. v. Agrigenetics LP Novartis AG, Eur. Pat. Off., T 1054/97 (2000), *available at* http://legal.european-patent-office.org/dg3/biblio/t971054eu1.htm (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).
[139] T 301/87, BIOGEN/Recombinant DNA, [1990] E.P.O.R. 190 (Eur. Pat. Off. (Technical Bd. App.) 1989).
[140] *Id.* at 210–211
[141] *Id.* at 207, 210.
[142] *Id.* at 210.
[143] *Id.* at 210–11.

products appeared to play an important role in the Board's nonobviousness determination.

In a separate *Biogen* decision relating to the same invention, the Board reiterated that a person skilled in the art would not have been able to isolate the specific DNA molecules by application of the common general knowledge.[144] Furthermore, the Board held that because the prior art suggested using a mixed probe, not a unique probe as used by the inventor, the prior art did not promise success to a skilled person faced with the technical problem set out in the patent, and therefore the claimed invention involved an inventive step.[145] Hence, the skepticism of skilled artisans before the invention apparently served as a secondary consideration in the Board's decision.

Furthermore, the Technical Board of Appeals found an inventive step when there was evidence of others' failure to produce the claimed invention.[146] The prior art taught bovine basic fibroblast growth factor ("bFGF") polypeptide.[147] The claims were directed to an isolated DNA encoding a mammalian bFGF polypeptide having a particular sequence.[148] Three companies in addition to the applicant, however, attempted to sequence bovine bFGF polypeptide, but all three failed to provide the correct or complete amino acid sequence.[149] Therefore, the Board concluded that sequencing the bovine bFGF polypeptide and isolating the DNA that encodes it must involve an inventive step.[150] This again suggests that secondary considerations may play a role in nonobviousness determinations relating to nucleic acid molecules in Europe.

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[144] T 500/91, BIOGEN/Alpha-interferon II, [1995] E.P.O.R. 69, 72 (Eur. Pat. Off. (Technical Bd. App.) 1992).
[145] *Id.* at 79–80.
[146] T 343/98, THE SALK INSTITUTE FOR BIOLOGICAL STUDIES/Fibroblast Growth Factor (Eur. Pat. Off. (Technical Bd. App.) 2001), *available at* http://legal.european-patent-office.org/dg3/pdf/t980343eu1.pdf *at* 13 (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).
[147] *Id.* at 8.
[148] *Id.* at 2.
[149] *Id.* at 9, 12.
[150] *Id.* at 13.

Similarly, the Board found that the lack of availability of a suitable library, and past failure with available libraries, was sufficient to find an inventive step.[151] The invention was directed to a full-length DNA encoding human protein C, and the prior art disclosed the isolation and characterization of a partial cDNA encoding human protein C that lacked the 5' end.[152] The Board held that although the skilled person would have readily undertaken to isolate a full-length DNA encoding human protein C using the partial cDNA of the prior art, the isolation of a full-length DNA depended on the availability of a good quality human liver cDNA library.[153] The fact that the prior art had failed to isolate a full length clone from their library confirmed the importance of the quality of the library.[154] Therefore, the isolation and characterization of the full length sequence involved an inventive step.[155]

So, although secondary considerations are not generally given as much weight in an inventive step analysis in Europe as they are in a nonobviousness analysis in the United States, they do appear to play some role in obviousness determinations for nucleic acid molecules.

D. Japan

1. Statutory Law

In addition to being bound by the TRIPS requirement for an inventive step, Japan is governed by Tokkyo Ho (Japan Patent Law) section 29(2):

> Where an invention could easily have been made, prior to the filing of the patent application, by a person with ordinary skill in the art to which the

[151] T 223/96, ELI LILLY/Protein C (Eur. Pat. Off. (Technical Bd. App.) 1999), *available at* http://legal.european-patent-office.org/dg3/pdf/t960223eu1.pdf *at* 26 (last visited May 29, 2004) (on file with the North Carolina Journal of Law & Technology).
[152] *Id.* at 1, 22–23.
[153] *Id.* at 24–26.
[154] *Id.* at 26.
[155] *Id.* at 27–28.

> invention pertains, on the basis of an invention or inventions referred to in any of the paragraphs of Subsection (1), a patent shall not be granted for such an invention notwithstanding Subsection (1).[156]

The current Japan Patent Law, including the inventive step requirement, was formulated and took effect in 1960.[157]

2. Relevant Prior Art

The cited prior art must be reasonably related to the inventor's field of technology in Japan.[158] Also, Japan only considers oral disclosures within its national boundaries.[159] Japan has a six month grace period, but it does not apply to the inventor's own published application, so there is effectively no grace period.[160] Secret prior art cannot be used as prior art for the determination of inventive step in Japan.[161]

3. Prima Facie Test

The Japanese Patent Office interprets Japan Patent Law section 29(2) to mean that a patent should only be granted for an improved invention showing remarkable progress over the prior art in terms of its purpose, constitution or effect.[162] The Japanese Patent Office Guidelines require that in order to make a rejection on the ground of lack of inventive step, the examiner must provide logical reasons why a person skilled in the art could easily have

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[156] *Japan*: Japan Patent Law § 29(2) (1959), *reprinted in* JOHN P. SINNOTT ET AL., 2F WORLD PATENT LAW AND PRACTICE 276 (rev. ed. 2004).
[157] Sekizo Hayashi, *Main Changes of Japanese Patent System and Important Decisions: In Chronological Order from 1960*, 27 A.I.P.P.I. 299, 300 (2002).
[158] David Abraham, *Shinpo-Sei: Japanese Inventive Step Meets U.S. Non-Obviousness*, 77 J. PAT. & TRADEMARK OFF. SOC. 528, 531 (1995).
[159] Czmus, *supra* note 17, at 459.
[160] *Id.*
[161] Saito & Sweeney, *supra* note 9, at 5–6.
[162] John Richards, *Recent Patent Law Developments in Asia*, 7 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 599, 620 (1997).

made the claimed invention.[163] The reasoning must be based on whether there is motivation towards the claimed invention.[164]

Determination of inventive step under the Japanese system typically consists of "1) analyzing the cited prior art; 2) comparing the claimed invention with the cited prior art; and 3) assessing the differences between the claimed invention and the cited prior art."[165] More specifically, the analysis requires one to:

(1) Identify the claimed invention and review the teachings of the prior art;
(2) Select the most suitable prior art for comparison with the invention;
(3) Compare the claimed invention with the selected prior art;
(4) Recognize the common and different features between the two without considering effects (or "koka");
(5) Establish a logical argument as to whether or not a person of ordinary skill in the art could have made the claimed invention at the time of filing on the basis of the features previously identified in the cited prior art and the invention;
(6) Judge whether sufficient motivation exists in the cited prior art to arrive at the claimed invention; and
(7) If sufficient motivation exists, the application lacks an inventive step.[166]

For highly advanced and complex technology, "a person with ordinary skill in the art" may be defined as "a team of experts from various fields."[167] As in the United States, the motivation for the invention provided by the patent examiner may differ from that of the applicant.[168] The Japan Examination Guidelines notes four possible types of motivation: "(1) close relation of technical fields;

[163] *Id.* at 620–21.
[164] *Id.* at 621.
[165] Saito & Sweeney, *supra* note 9, at 5.
[166] Abraham, *supra* note 158, at 529–30.
[167] Saito & Sweeney, *supra* note 9.
[168] Abraham, *supra* note 158, at 531.

(2) close similarity of problem to be solved; (3) close similarity of the function and working mechanisms; or (4) suggestions in the contents of the cited prior art."[169]

In Japan, there has been no court decision regarding inventive step as it applies to nucleic acid molecules. There was, however, an infringement suit based on patents to recombinant human tissue plasminogen activator ("t-PA").[170] The accused infringer produced a modified recombinant t-PA, wherein the valine at amino acid position 245 was replaced with methionine.[171] The court noted that it was possible for the average skilled person to produce t-PA variants, that amino acid position 245 is in the hydrophobic region not important for biological activity, and that the mutation of valine to methionine had no effect on the function of the protein and did not exhibit better properties.[172] The court held that the t-PA of the accused infringer constituted an equivalent of the patented recombinant t-PA, and therefore infringed the patent.[173]

For nucleic acids, the Japan Patent Office has found it difficult to apply the standard that is typically used for assessing obviousness of chemicals, namely based on the similarity or non-similarity of chemical structures.[174] Because DNA is composed of four common nucleotides, its chemical structure, and hence its chemical properties, has no essential characteristic.[175] In addition, there is not a clear correlation between the chemical structure of the DNA and the activity of the encoded protein.[176] Hence, the Japan Patent Office has found it difficult to make a presumption of structural obviousness for nucleic acid molecules as for

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[169] Saito & Sweeney, *supra* note 9, at 6.
[170] Genentech Inc. v. Sumitomo Pharm. Co. Ltd., 28 IIC: INT. REV. INDUS. PROP. & COPYRIGHT L. 391 (1997) (English translation of Osaka High Ct. decision).
[171] *Id.* at 391.
[172] *Id.* at 392–93.
[173] *Id.* at 394.
[174] Yusuke Hiraki, *Patentability Requirements and Scope of Protection of Expressed Sequence Tags (ESTs), Single Nucleotide Polymorphisms (SNPs) and Entire Genomes*, 25 A.I.P.P.I. J. 10, 13 (2000).
[175] *Id.* at 14.
[176] *Id.*

conventional-type chemicals.[177] The assessment of obviousness, therefore, is generally based on the ease of the process of obtaining the nucleic acids.[178] The Japan Patent Office applies a presumption of obviousness based on the process, i.e. DNA molecules are presumed to be obvious based on prior art teachings showing standard processes for their isolation, even if no structurally analogous compounds are disclosed in the prior art.[179] If evidence of the difficulties of the processes are provided, then the DNA molecules may be determined to be non-obvious.[180] When a gene is isolated and characterized that codes for a known protein, even if the amino acid sequence of the protein is not disclosed in the prior art, there may not be an inventive step.[181] As a consequence, patents to nucleic acid molecules are frequently denied based on lack of inventive step.[182] Generally, it is the view in Japan that if patents to nucleic acids are obtained too easily, free research and development may be inhibited, which is contrary to the objective of the patent system.[183]

The Japan Implementing Guidelines of 1997 ("Guidelines") sets forth examples of the assessment of inventive step as it applies to nucleic acid molecules.[184] For example, an isolated human polynucleotide encoding a polypeptide with 80% similarity to a known rat polypeptide and without any advantageous effect lacks inventive step because it is common general knowledge to isolate a human DNA encoding a particular protein using a DNA encoding the same protein from another mammal as a probe.[185] Similarly, a human polynucleotide isolated from a liver cDNA library that is

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[177] *Id.*
[178] *Id.* at 13.
[179] *Id.* at 15.
[180] *Id.*
[181] Richards, *supra* note 162, at 624.
[182] Hiraki, *supra* note 174, at 16.
[183] *Id.* at 20.
[184] JAPAN PATENT OFFICE, JAPAN IMPLEMENTING GUIDELINES: EXAMPLES OF EXAMINATIONS ON THE INVENTIONS RELATED TO GENES (DNA FRAGMENTS, FULL-LENGTH cDNAs, AND SINGLE NUCLEOTIDE POLYMORPHISMS) (1997), *available at* http://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/dnas.htm (last visited Nov. 16, 2004) (on file with the North Carolina Journal of Law & Technology).
[185] *Id.* at 6, Case 6.

part of a structural gene of unknown function lacks inventive step because it is well-known to prepare cDNA libraries from human organs and to randomly isolate and sequence DNAs therefrom.[186]

The Guidelines also set forth rules for application of inventive step to nucleic acid sequences as follows: (1) a nucleic acid encoding a protein has an inventive step if the protein has an inventive step; (2) if the protein is known but its amino acid sequence is not, the nucleic acid encoding the protein does not have an inventive step if a person skilled in the art could easily determine the amino acid sequence; (3) when the amino acid sequence of the protein is known, the nucleic acid encoding the protein does not have an inventive step; (4) when a nucleic acid is known, a mutant of said nucleic acid which has the same properties and functions does not have an inventive step.[187] The Guidelines further state that if the amino acid sequence of the protein is known, then it would be easy to try to isolate and characterize a nucleic acid encoding the protein by well-known, conventional cloning techniques.[188] The invention will be denied for lack of inventive step based on the grounds of obviousness because patenting of such nucleic acids would interfere with technological development.[189]

4. Secondary Criteria

In Japan, "koka," or secondary considerations, especially unexpected results or commercial success, are considered in obviousness determinations.[190] The koka are a critical element in establishing patentability in Japan.[191] For example, in *Genentech*, the Court held that the mutation of valine to methionine did not

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[186] *Id.* at 6–7, Case 7.
[187] Yusuke Hiraki, *Current Development in Biotech Patents in Japan*, 22 A.I.P.P.I. J. 151, 159 (1997).
[188] *Id.* at 159–60.
[189] *Id.* at 160.
[190] Abraham, *supra* note 158, at 532–33.
[191] *Id.* at 534.

result in a protein exhibiting better properties, and hence constituted an equivalent of the patented recombinant t-PA.[192]

The Japanese Patent Office Guidelines require that in order to make a rejection on the ground of lack of inventive step, the examiner must consider whether any advantageous effects occur over the prior art.[193] A DNA molecule may be non-obvious if evidence of the unpredictable advantages of the DNA molecule is provided.[194] When a DNA molecule is isolated and characterized that codes for a known protein there may be an inventive step if the isolated DNA molecule has some advantage over other DNA molecules encoding the known protein.[195] According to the Guidelines, an isolated human polynucleotide encoding a polypeptide with 80% similarity to a known rat polypeptide may have an inventive step if the DNA has an unexpected advantageous effect.[196] In addition, each of rules (2), (3), and (4) for application of inventive step to nucleic acid sequences specify that if the nucleic acid has an advantageous effect as compared to other nucleic acids encoding the protein, then the nucleic acid has an inventive step.[197] An invention will not be denied for lack of inventive step if the isolated nucleic acid has a remarkable effect.[198]

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[192] Genentech Inc. v. Sumitomo Pharm. Co. Ltd., 28 IIC: INT. REV. INDUS. PROP. & COPYRIGHT L. 392–94 (1997) (English translation of Osaka High Ct. decision).

[193] Richards, *supra* note 162, at 620–21.

[194] Hiraki, *supra* note 174, at 15.

[195] Richards, *supra* note 162, at 624.

[196] JAPAN PATENT OFFICE, JAPAN IMPLEMENTING GUIDELINES: EXAMPLES OF EXAMINATIONS ON THE INVENTIONS RELATED TO GENES (DNA FRAGMENTS, FULL-LENGTH cDNAs, AND SINGLE NUCLEOTIDE POLYMORPHISMS) 7, Case 7 (1997), *available at* http://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/dnas.htm (last visited Nov. 16, 2004) (on file with the North Carolina Journal of Law & Technology).

[197] Hiraki, *supra* note 187, at 159.

[198] *Id.* at 160.

E. Primary Differences between United States, Australia, Europe and Japan

Above, it has been shown that Australia, the United States, Europe and Japan all have different means and thresholds for assessing obviousness or inventive step. Although TRIPS provides minimum standards for implementing countries to follow, each individual nation is free to set stricter standards than those required under TRIPS. Hence, the obviousness or inventive step requirement under TRIPS Article 27(1) may be interpreted differently under different national laws.

Prior art is interpreted under all the national laws to include everything that is known, published and available to the public, provided it is in an analogous field to the invention; however, only the United States and Australia allow application of secret prior art. The United States, Australia and Japan restrict oral disclosures to only those that occur within their national boundaries, whereas Europe allows oral disclosures from anywhere in the world. Only the United States provides a one year grace period within which the inventor may publish before filing a patent application. Whereas the number of references that can be combined in the United States is not limited, the use of more than two references in Europe rarely occurs.

Japan and the United States use similar approaches in determination of inventive step. Namely, they ask: "(1) what is the prior art? (2) what are the differences between [the] claimed invention and the prior art? and (3) would the invention be obvious to a person with ordinary skill in the art?"[199] In contrast, Europe's approach is significantly different. Namely, they ask: "(1) what is the closest prior art? (2) what is the objective problem solved by the invention? and (3) was the solution reached by the invention obvious to a person with ordinary skill in the art?"[200] Australia similarly employs a problem-solving approach and faces the consequent dangers of hindsight. Japan and the United States consider all the features of the claimed invention, whereas Europe

[199] Saito & Sweeney, *supra* note 9, at 6–7.
[200] *Id.*

considers only those features that contribute to the solution.[201] A person of ordinary skill in the art may be "a team of experts" in Japan and Europe, but not in the United States.[202]

With respect to nucleic acid molecules, only the United States uses a structural obviousness standard analogous to the chemical arts. Australia, Japan, and Europe all consider the obviousness of the method of isolation of the claimed nucleic acid molecules. The United States applies the lowest bar for obviousness, finding that virtually any novel nucleic acid sequence is nonobvious. Australia, although considering the obviousness of the method of isolation, also has a relatively low bar for obviousness. Europe and Japan, in contrast, have a much higher bar for obviousness, requiring evidence of significant difficulties in the isolation procedure, or evidence of unexpected properties of the nucleic acid molecules. As a consequence, Europe has tended to find lack of inventive step much more frequently than the Federal Circuit or the Board of Appeals and Interferences in the United States. Although Australia likewise evaluates obviousness of nucleic acids based on the obviousness of the methods of their isolation, Europe generally recognizes a higher threshold for inventive step than does Australia. This may, in part, be due to the almost unavoidable hindsight analysis which occurs with the European method of assessing inventive step, or it may be due to a higher skill level attributed to a person of ordinary skill in the art in Europe.

Secondary criteria, such as commercial success, failure or skepticism of other skilled artisans, and unexpected results or properties, generally have more weight in the United States;[203] however, secondary considerations have played some role in nonobviousness analysis for nucleic acid molecules in Australia, Europe and Japan. For example, Australia has considered the failure of others in at least one court decision. The European Technical Board of Appeals has considered surprising technical effects, unexpected properties, skepticism of skilled artisans, and failure of skilled artisans in inventive step determinations for

[201] *Id.* at 7.
[202] *Id.*
[203] Saito & Sweeney, *supra* note 9, at 7.

nucleic acid molecules. In Japan, koka have also played an important role in inventive step analysis for nucleic acid molecules. The Japan Patent Office has routinely considered the unexpected, advantageous or remarkable effects of newly isolated and characterized nucleic acid molecules before determining if there is an inventive step.

III. The Implications of Having Different Legal Standards

Because the obviousness or inventive step requirement has been characterized as the ultimate bar to patentability, the impact of a low or high threshold for nucleic acid molecules is significant. Differences in obviousness standards may be attributable to or complementary to other differences in national patent law. For example, it has been suggested that such differences may relate to the presence of the first-to-file versus the first-to-invent system, to the availability of pre-grant opposition, and to the availability of compulsory licensing.[204] The ultimate goal of patentability standards, and consequently obviousness standards, is to promote research and development. Where the obviousness line is drawn, therefore, may have a significant impact on either stimulation or retardation of invention. The rationale for the obviousness requirement is that most technological advances occur incrementally.[205] When rapid scientific advances occur, they generally serve first to expand and then to contract the boundaries of patentable subject matter, as the new research tools gradually become technologically mundane.[206] As methods of gene isolation and characterization become more routine, therefore, obviousness becomes harder to avoid.[207]

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[204] Jerry Koopman, *The Patentability of Transgenic Animals in the United States of America and the European Union: A Proposal for Harmonization*, 13 FORDHAM INTELL. PROP. MEDIA & ENT. L. J. 103, 192–93 (2002).

[205] Donna M. Gitter, *International Conflicts over Patenting Human DNA Sequences in the United States and the European Union: An Argument for Compulsory Licensing and a Fair-Use Exemption*, 76 N.Y.U. L. REV. 1623, 1673 (2001).

[206] Reid G. Adler, *Genome Research: Fulfilling the Public's Expectations for Knowledge and Commercialization*, 257 SCIENCE 908, 911 (1992).

[207] Gitter, *supra* note 205, at 1673.

If improper, a patent law system and its component obviousness threshold may actually retard research and development.[208] If the inventive step requirement is too easily satisfied, patents are granted for inventions that have little or no inventive merit.[209] A proliferation of intellectual property rights upstream may ultimately stifle research and development downstream.[210] Consequently, more upstream patent rights may lead to fewer useful products in biotechnology.[211] The key is to properly distribute the incentives between basic researchers and applied technicians in order to optimize overall research and development.[212] Raising the bar on when the patent criteria are satisfied is one way to remove impediments to access to research tools and techniques.[213] Hence, obviousness standards play a critical role in affecting access to research materials and the extent of secondary innovation. According to Coase's theorem, the initial allocation of property rights does not matter because property rights will be licensed to whomever can make the most productive use of the property rights; however, Coase's theorem does not apply when property rights are initially allocated improperly.[214] Furthermore, whereas Coase's theorem assumes zero transaction costs, researchers in biotechnology rely heavily on prior research.[215]

Gene patents may hinder basic research and commercial exploitation of inventions by hindering access to technology.[216] The precise impact of gene patents depends on the market niche that the inventor occupies in the biotechnology industry.[217] Whereas pioneers must be guaranteed some return for their

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[208] Nicol & Nielsen, *supra* note 76, at 374.
[209] *Id.* at 365.
[210] Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 701 (1998).
[211] *Id.*
[212] Charles R. McManis, *Re-Engineering Patent Law: The Challenge of New Technologies*, 2 WASH. U. J.L. & POL'Y 1, 15 (2000).
[213] Nicol & Nielsen, *supra* note 76, at 363.
[214] Rai, *supra* note 60, at 839.
[215] *Id.*
[216] Nicol & Nielsen, *supra* note 76, at 359.
[217] *Id.*

investment, improvers may be inhibited by patents that block access to essential research tools.[218] As a consequence of the relaxed standards for obviousness of nucleic acid molecules imposed by the Federal Circuit, the risk-reward models for investment in biotechnology research are currently different than for traditional pharmaceutical research.[219] It has been suggested by some that the relaxed requirements may promote upstream innovation, at a substantial cost to downstream innovation.[220] New inventors in upstream innovation require less capital investment and achieve faster time to market.[221] It has also been argued, however, that when the obviousness standard is low, first inventors are not able to obtain the broad patent rights they deserve, and patent rights are widely afforded to copied inventions.[222]

Obviousness analysis of nucleic acid molecules may be unique by virtue of the nature of the biotechnology industry.[223] Because there are many small biotechnology companies whose only asset is intellectual property, broad cross-licensing is unlikely to happen.[224] When many inventors own small, overlapping slices of the same pie, a breakdown in the intellectual property system can occur.[225] For example, where there are multiple monopolies controlling components of a product, the price is higher than if a single company controlled all the components, resulting in a "patent thicket."[226] The "tragedy of the anticommons" may result when multiple owners have a right to exclude others from a scarce resource such that the resource becomes underutilized.[227] If too many owners hold rights to upstream research, as in a country with

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[218] *Id.*
[219] McManis, *supra* note 212, at 15.
[220] *Id.* at 4–5.
[221] *Id.* at 15.
[222] Rai, *supra* note 60, at 838–40.
[223] *See, e.g.*, Antonio Regalado, *The Great Gene Grab*, Sep.-Oct. TECH. REV. 48, 53 (2000).
[224] *Id.*
[225] *Id.*
[226] Carl Shapiro, *Navigating the Patent Thicket: Cross-Licenses, Patent Pools and Standard-Setting*, *in* 1 INNOVATION POLICY AND THE ECONOMY 119, 122–123 (Adam B. Jaffe et al. eds., 2000).
[227] Heller & Eisenberg, *supra* note 210, at 698–99.

a lower obviousness bar like the United States, it may present obstacles to future research, especially if access to multiple patented inventions is required to create a downstream product.[228] In some areas of technology, patent pools have emerged with the help of government, when multiple licenses are required to develop new products.[229] However, high transaction costs may present an impediment to the bundling of intellectual property rights in biotechnology.[230] Licensing costs are frequently very high in biotechnology because it is difficult to estimate the value of an invention.[231] Also, owners of intellectual property rights in biotechnology are diverse and have different interests—they may consist of federal agencies, academic institutions, or private companies—and therefore would likely face difficulty in reaching agreement on a licensing policy.[232]

Patentability determinations, in addition to being determinations on how to balance property rights among inventors, are also determinations on how to balance property rights with the public domain.[233] Patent applicants in Japan tend to file applications more for defensive purposes, that is, to prevent anyone else from getting a patent, than to enforce property rights.[234] Historically, the intended beneficiary of a patent in Japan has been the user of the patented invention, not the patent holder.[235] Consequently, patent seekers from the United States often complain that the Japanese patent system is very weak.[236] In the United States, in contrast, the essential purpose of a patent is to protect the patentee, and hence claims are interpreted broadly and patent rights are determined based on first to invent.[237] In Japan, the role of the patent system is to teach industry new innovations

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[228] *Id.*
[229] *Id.* at 700.
[230] *Id.*
[231] Rai, *supra* note 60, at 840.
[232] *Id.* at 841.
[233] *Id.* at 844.
[234] McManis, *supra* note 212, at 6.
[235] *Id.*
[236] *Id.*
[237] Samson Helfgott, *Cultural Differences between the U.S. and Japanese Patent Systems*, 72 J. PAT. & TRADEMARK OFF. SOC. 231, 232–33 (1990).

and encourage industrial development.[238] There is a deferred examination system, frequently delays in examination, and narrow interpretation of claims.[239] Industry is free to make slight modifications or to make improvements to avoid infringement and may even file patent applications on the slightly modified inventions.[240] Furthermore, the practice of "patent flooding," that is, "filing many patents to surround [patented] technology," is common in Japan.[241] Patent holders of improvements over pioneering technology may force the patent holder of the pioneering invention to cross-license by virtue of the compulsory license laws in Japan.[242]

With respect to nucleic acid molecules, Japan has generally also exercised greater concern for protecting the public domain than for protecting the property rights of inventors, whereas the United States has applied obviousness to nucleic acid molecules in a way that dramatically lowers the bar for patentability and impoverishes the public domain.[243] The issue of obviousness and nucleic acid molecules has produced a split between the public and the private domain.[244] Public sector and nonprofit researchers advocate strict application of the nonobviousness standard and avoiding broad patent protection.[245] On the other hand, biotechnology companies argue that broad patent protection is necessary to encourage innovation and stimulate biotechnology research and development.[246] The issue has divided public sector and nonprofit researchers from biotechnology companies, and this conflict transcends national boundaries.[247]

The effect of TRIPS may be to shift the boundary between the public good and private interest in favor of private interest.[248]

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[238] *Id.* at 234.
[239] *Id.*
[240] *Id.*
[241] Abraham, *supra* note 158, at 536.
[242] *Id.*
[243] Rai, *supra* note 60, at 833.
[244] Gitter, *supra* note 205, at 1677.
[245] *Id.*
[246] *Id.* at 1677–78.
[247] *Id.* at 1673–74.
[248] Lawson, *supra* note 7, at 386.

Providing for widespread patenting of biotechnology inventions such as nucleic acid molecules may result in a reduction in the number of producers to primarily multinational corporations.[249] This is of particular concern to those nations, like Australia, with endemic genetic diversity. Genetic diversity is a valuable genetic resource in Australia, with about 1 million species of animals, plants and microbes.[250] The value of the rich genetic resources is contained in the differences within and between genes.[251] Such genetic diversity serves as a potential source of nucleic acid molecules for inventions in the agricultural and pharmaceutical industries.[252] The broad claims to nucleic acid molecules that are typically issued in Australia may impose limits on subsequent patentable subject matter and may fail to value the wide benefits of nucleic acid molecules by restricting the full potential to exploit genetic diversity.[253] The obviousness standard in Australia, therefore, may not be generating the maximum benefit from the grant of patent monopolies and may not be extracting the full potential for Australians from its unique genetic resources.[254]

The TRIPS agreement does not require other countries to adopt the same standard of obviousness for nucleic acid molecules as the United States, that is, a relatively generous view of obviousness.[255] A country implementing TRIPS could establish a narrow view of obviousness, raising the bar for patentability. Fewer patents would be granted and more subject matter would remain in the public domain.[256] Alternatively, a country could implement a standard of obviousness like the United States, thereby lowering the bar for patentability, and allowing patents to be granted for second or third generation innovators.[257] If countries with significant biotechnology research and development were to establish a higher bar for patentability for nucleic acid

[249] Verma, *supra* note 6, at 349.
[250] Lawson, *supra* note 7, at 374.
[251] *Id.*
[252] *Id.* at 373–74.
[253] *Id.* at 383.
[254] *Id.* at 386.
[255] Petherbridge, *supra* note 2, at 1055–56.
[256] *Id.*
[257] *Id.* at 1056.

molecules, they could create a competitive advantage over the United States, Europe, or Japan.[258] This would preserve subpatentable information in the public domain in countries that have been excluded by leading patent countries, allowing the information to be used for development of next generation products.[259] It would also encourage foreign and domestic investment, leading to transfer of research and development from leading patent countries to other countries, especially if labor costs are low and a biotechnology skill base is present.[260]

A considerable concern with having different obviousness standards for nucleic acids in different countries is that such may impede sharing of information among researchers in different countries.[261] Furthermore, imbalances between United States and foreign patent laws create uncertainties that impede the biotechnology industry's ability to plan for and conduct research and development.[262] This is compounded by differences in the extent of research and development in different countries. Currently, over ninety percent of global patent activity occurs in Europe, the United States, and Japan.[263] In Australia, the majority of patent applicants are foreign, from the United States, Japan and Europe, whereas only about two percent of patent applications in biotechnology originate in Australia.[264] Consequently, Australian companies and companies from other countries with less biotechnology research are forced to seek licenses from foreign companies from countries with substantial biotechnology research.[265]

On the other hand, United States biotechnology companies aggressively seek patent protection in Europe and other countries in order to recoup the significant investment associated with biotechnological research.[266] The United States has alleged wide-

[258] *Id.* at 1059.
[259] *Id.* at 1060.
[260] *Id.* at 1061.
[261] Leslie Roberts, *Genome Patent Fight Erupts*, 254 SCIENCE 184, 186 (1991).
[262] Adler, *supra* note 206, at 909.
[263] Saito & Sweeney, *supra* note 9, at 9.
[264] Nicol & Nielsen, *supra* note 76, at 360–61.
[265] *Id.* at 363.
[266] Gitter, *supra* note 205, at 1691.

scale losses due to weak intellectual property protection and wide-scale piracy of intellectual property rights in newly industrializing countries, resulting in a loss in research and development investments.[267] Under the WTO, all member states are bound by the Understanding on Rules and Procedures Governing the Settlement of Disputes.[268] The United States has identified Australia as a trading partner that fails to provide adequate intellectual property protection for United States companies.[269] As a consequence, Australia is now open to challenge under the WTO dispute mechanisms if, for example, it employs different patentability standards for nucleic acid molecules as compared to other subject matter.[270]

IV. Conclusion

Obviously a global patent system with a unified standard for patentability for nucleic acid molecules would be preferable to the current system of different national patent standards.[271] It is possible that harmonization in examination could be reached much more easily if the standard for obviousness was not too high because then business factors would not have as great an impact on the examination process.[272] The patent offices could apply a low level standard for obviousness for nucleic acid molecules in *ex parte* procedures and leave the business world and courts to consider full scale obviousness by *inter partes* procedures.[273] It is also possible that an international compulsory licensing system that harmonizes national laws could reduce the danger of the race to patent nucleic acid molecules imperiling international scientific collaboration.[274] In the mean time, as long as obviousness standards for nucleic acid molecules differ among nations, the

[267] Verma, *supra* note 6, at 333–34.
[268] Lawson, *supra* note 7, at 384.
[269] *Id.* at 384–85.
[270] *Id.* at 386.
[271] Saito & Sweeney, *supra* note 9, at 9.
[272] Sekizo Hayashi, *Comparative Study on Patent Systems Between the US and Japan (IV)—Obviousness*, 25 A.I.P.P.I. J. 131, 138 (2000).
[273] *Id.*
[274] Gitter, *supra* note 205, at 1683–84.

differences, and even inequities, in distribution of property rights between pioneering and secondary inventors, and between the public and private domain will remain. Likewise, there will remain a persistent barrier to international research collaboration and a lack of free flow of information between inventors from different countries, and inventors from different countries will continue to be able to opportunistically exploit the differing obviousness standards.