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Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial cDNA Sequences

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OPINION LETTER AS TO THE PATENTABILITY OF CERTAIN INVENTIONS ASSOCIATED WITH THE IDENTIFICATION OF PARTIAL cDNA SEQUENCES

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I. INTRODUCTION

You have asked for our legal opinion on the patentability of inventions claimed in U.S. patent applications 07/716,831, filed June 21, 1991 (the '831 application, or "'831"), 07/837,195, filed September 25, 1992 ("'195"), and 07/952,911, filed February 12, 1993 ("'911"), all filed in the name of Craig Venter and others and assigned to the National Institutes of Health "(NIH)."

We understand that NIH has abandoned these patent applications and has no present intention of filing similar applications in the future, but that NIH remains interested in the patenting of human DNA sequences from a broader public policy perspective. We have therefore attempted to focus on issues that are likely to recur in other patent applications filed by other people and institutions involved in DNA sequencing rather than on questions that are peculiar to the facts of these particular applications. Nonetheless, we preface this opinion letter with the caution that the facts of each patent case are unique. We have before us for consideration only these three NIH filings, and we are not in a position to offer a definitive opinion on the patentability of other inventions that may be claimed by other parties and supported by different disclosures in different patent applications.

The expertise we bring to this issue is legal rather than scientific. Many issues of patent law turn on the understanding of skilled practitioners working in the field of the invention. We have identified these issues throughout this letter.

We begin with a brief description of the NIH patent applications and then turn to the patentability issues presented by these applications. In our view, the most significant of these issues concern the utility, nonobviousness, and disclosure requirements of the patent laws.

II. THE NIH cDNA PATENT APPLICATIONS

The three applications under review seek patent protection for inventions associated with the identification of approximately 6,800 partial cDNA sequences, called "expressed sequence tags" ("ESTs") in the applications, in the laboratory of Dr. Craig Venter at the National Institute of Neurological Disorders and Stroke prior to his departure from NIH in July 1992. These sequences, which are typically 150-400 base pairs in length, were obtained by partially sequencing randomly selected clones from human brain cDNA libraries enriched by removing ribosomal and other common

sequences. The applications include many different claims, which for convenience we divide into the following groups:

- *Sequence* claims (claims 1-3, 17-18, and 25-43 in the '195 application, and 1-3 and 19-20 in the '911 application)
- *Full gene* claims (claims 4-18 and 47-54 in the '195 application and 4-16 in the '911 application)
- *Purified form* claims (claims 19 in the '195 application and 21 in the '911 application)
- *Construct* claims (claims 20-21 in the '195 application and 22-23 in the '911 application)
- *Panel* claims (claim 22 in the '195 application and 24 in the '911 application)
- *Antisense* claims (claims 23 in the '195 application and 25 in the '911 application)
- *Triple helix* claims (claims 24 in the '195 application and 26 in the '911 application)

The '831 application, which initially covered the first 315 ESTs as well as the method for obtaining them, was subsequently converted into a statutory invention registration covering only the method claims before being rejected by the patent examiner. We do not address the patentability of the method claims except insofar as it relates to the patentability of the other claims. The sequences of the '831 application are included in the 2,421 sequences covered by the '195 application, which is a continuation-in-part of '831. The claims of '195 were finally rejected by the Patent and Trademark Office ("PTO") in August of 1993. The claims of the '911 application, covering an additional 4,448 sequences, were rejected by the PTO in a first office action in December of 1993. NIH abandoned all three applications in February of 1994.

III. UTILITY

Perhaps the issue that has drawn the most attention in public discussions of the patentability of the NIH cDNA sequences is whether these sequences have patentable utility.

A. *Background And Applicable Law*

The U.S. Constitution authorizes Congress to provide patent protection for the express purpose of promoting progress in "the useful arts."[1] In keeping with this language, the U.S. patent statute limits patent protection to "useful" inventions[2] and requires patent applicants to disclose how to use their inventions.[3] The utility requirement has at least three interrelated dimensions to it, although the courts and the PTO are not always clear about which of these dimensions is at issue in a given case. First, an invention must serve a practical purpose.[4] Second, it must be "operable," or capable of use.[5] Third, the invention as claimed must be supported by a disclosure that is adequate to enable a skilled practitioner working in the field to use the invention with no more than routine experimentation.[6]

One source of difficulty in defining the content of the utility requirement is a lack of clarity as to its underlying purposes. In the early nineteenth century, Justice Story suggested that the standard of utility should be considered satisfied so long as an invention has some beneficial use and is not "frivolous or injurious to the well-being, good policy, or sound morals of society."[7] As long as the invention was not contrary to public morality and policy, Story saw no reason why the public should object to the patenting of an invention of very little utility: "If it be not extensively useful,

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[1] U.S. CONST. art. I, § 8, cl. 8.

[2] 35 U.S.C. § 101 (1988).

[3] 35 U.S.C. § 112 (1988).

[4] Anderson v. Natta, 480 F.2d 1392, 178 U.S.P.Q. (BNA) 458 (C.C.P.A.) 1973). *See* 1 W. ROBINSON, TREATISE ON THE LAW OF PATENTS FOR USEFUL INVENTIONS (1890).

[5] Newmann v. Quigg, 877 F.2d 1575, 11 U.S.P.Q.2d (BNA) 1340 (Fed. Cir. 1989).

[6] 35 U.S.C. § 112 (1988).

[7] Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8,568).

it will silently sink into contempt and disregard."[8] In this view the utility requirement merely serves to withhold patents on harmful inventions, and it is the function of the market to limit the value of patents on inventions of only minimal utility.

This was probably the dominant view of the utility requirement in the United States through the middle of the twentieth century, except in the case of inventions claimed to have value in the treatment of human disease. Such inventions were subjected to a higher standard of proof of utility, particularly in the days before the safety and efficacy of pharmaceutical products were separately monitored by the Food and Drug Administration, on the ground that issuance of a patent might mislead the public by appearing to represent a government imprimatur of the value of a so-called "patent medicine."[9] Modern courts have explicitly disclaimed this higher standard of utility for pharmaceuticals,[10] yet the double standard seems to live on as a practical matter, as will become apparent from a review of the cases.

The U.S. Supreme Court suggested a larger role for the utility requirement in *Brenner v. Manson.*[11] The invention at issue in that case was a new process for making certain known steroids. The patent examiner rejected the claims on the ground that the applicant had failed to disclose any utility for the chemical compounds produced by the process. The Board of Appeals within the Patent Office affirmed the rejection, but the Court of Customs and Patent Appeals reversed, holding that an operative process for producing a known product satisfies the utility requirement so long as the product is not alleged to be detrimental to the public interest. The Supreme Court reversed again in an opinion that raised at least as many questions as it answered about the utility requirement.[12]

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[8] *Id.*

[9] Mahler v. Animarium Co., 111 F. 530, 537 (8th Cir. 1901).

[10] *In re* Langer, 503 F.2d 1380, 183 U.S.P.Q. (BNA) 689 (C.C.P.A. 1974).

[11] 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[12] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

The Court explicitly rejected the view that the utility requirement is met by any invention that is not positively harmful to society.[13] Nor was utility established by showing that the invention yields products that are currently the subject of serious scientific investigation.[14] The court was particularly concerned that conferring patent rights in basic research discoveries could create "a monopoly of knowledge" and "confer power to block off whole areas of scientific development, without compensating benefit to the public."[15] The court concluded that patent protection was premature until the invention had been refined and developed to the point where "specific benefit exists in currently available form."[16] The majority opinion closed with the following passage: "A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. 'A patent system must be related to the world of commerce rather than to the realm of philosophy. . . .'"[17] One plausible reading of this opinion is that the utility requirement serves a timing function, leaving basic research discoveries in the public domain until they have yielded tangible benefits and have thereby left "the realm of philosophy" and entered "the world of commerce."

Whether or not there was a meaningful distinction to be drawn between the realm of philosophy and the world of commerce in the field of steroid chemistry in the 1960s, it is a very difficult distinction to maintain in biotechnology in the 1990s, with researchers in government and university laboratories seeking patent protection for their discoveries and with private firms developing research tools for commercial sale. In this environment, research discoveries that are the subject of serious scientific investigation may be sold commercially to researchers long before they have ripened into products for sale to the general public. How far must an inventor go to establish that such an invention offers a "specific benefit . . . in currently available form?"

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[13] *Id.* at 533, 148 U.S.P.Q. (BNA) at 695.

[14] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[15] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[16] *Id.* at 534-35, 148 U.S.P.Q. (BNA) at 695.

[17] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696 (quoting *In re* Ruschig, 343 F.2d 965, 970, 145 U.S.P.Q. (BNA) 274, 279 (C.C.P.A. 1965)).

This question has been particularly difficult to answer for pharmaceutical inventions, which often involve separately discovered products and uses. Decisions of the U.S. Court of Appeals for the Federal Circuit and its predecessor, the U.S. Court of Customs and Patent Appeals, have upheld the sufficiency of disclosures of pharmacological activity *in vitro* as establishing the practical utility of a novel compound.[18] In *Cross v. Iizuka*, the Federal Circuit acknowledged that "*in vitro* testing is but an intermediate link in a screening chain which may eventually lead to the use of the drug as a therapeutic agent in humans," but nonetheless concluded that this link was sufficient to establish a practical utility for the compound, noting: "Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility."[19] This suggests a more hospitable attitude toward the patenting of early stage pharmaceutical inventions than would be supported under a strict reading of *Brenner v. Manson*.

However, in recent years biotechnology patent practitioners perceived an increasing strictness on the part of the PTO in its application of the utility requirement, particularly in the context of claims to methods of treatment or to pharmaceutical compositions. A series of decisions from the PTO Board of Patent Appeals and Interferences ("the Board") reflects this trend,[20] which may finally be coming to an end in light of very recent developments in the PTO and the Federal Circuit.[21]

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[18] Cross v. Iizuka, 753 F.2d 1040, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985); Nelson v. Bowler, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[19] *Cross*, 753 F.2d at 1051, 224 U.S.P.Q. (BNA) at 748.

[20] *See, e.g., Ex parte* Sudilovsky, 21 U.S.P.Q.2d (BNA) 1702 (Bd. Pat. App. & Interf. 1992); *Ex parte* Aggarwal, 23 U.S.P.Q.2d (BNA) 1334 (Bd. Pat. App. & Interf. 1991); *Ex parte* Balzarini, 21 U.S.P.Q.2d (BNA) 1892 (Bd. Pat. App. & Interf. 1991).

[21] These recent developments are the publication of new Utility Examination Guidelines by the PTO, PTO Utility Examination Guidelines, 60 Fed. Reg. 36,263 (1995), and the decision of the Federal Circuit in *In re* Brana, 51 F.3d 1560, 34 U.S.P.Q.2d (BNA) 1436 (Fed. Cir. 1995), both discussed *infra*.

In *Ex parte Balzarini*,[22] the Board affirmed a rejection for lack of utility of claims to pharmaceutical compositions in unit dosage form comprising one of two specified ingredients that had shown antiviral activity against HIV *in vitro*. The Board agreed with the examiner that those skilled in the art would regard the *in vitro* tests as a useful screening tool for selecting which compounds are appropriate candidates for further testing, but nonetheless held that the applicants had failed to satisfy their further burden of demonstrating that those skilled in the art would accept the *in vitro* test results as predictive of *in vivo* efficacy in treating humans who are HIV positive or suffering from AIDS. The Board was careful to note that it was not necessarily requiring clinical testing in humans to establish utility, although it could be that nothing short of human clinical trials would satisfy those skilled in this particular art that the claimed inventions would be effective *in vivo*.[23]

In *Ex parte Aggarwal*,[24] the Board affirmed the examiner's rejection of broad claims to a method of treatment of tumors in animals by administering a therapeutically effective amount of recombinantly produced lymphotoxin. The specification described preparation of recombinant lymphotoxin and demonstration of *in vivo* activity in mice as well as *in vitro* activity. The examiner took the position that given the unpredictability of the treatment of tumors at the time of the filing, the limited test data of record were insufficient to demonstrate utility across the broad range of the claims. In affirming, the Board conceded that "[t]here is no question that appellants have made an important discovery with regard to chemical compounds (proteins) which are the subject of serious scientific investigation but of unverified and speculative utility."[25] The applicant argued unsuccessfully that the public interest called for allowing the filing of a patent application on such an invention early rather than waiting for what may be a long period of experimentation. According to the Board, in light of *Brenner v. Manson* and subsequent caselaw, such an application is premature until the applicant "can provide evidence showing substantial activity in screening

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[22] 21 U.S.P.Q.2d (BNA) at 1892.

[23] *Id.* at 1897.

[24] 23 U.S.P.Q.2d (BNA) at 1334.

[25] *Id.* at 1339.

tests customarily used and accepted as predicative [sic] of human activity for the type of chemical tested" and "commensurate with the scope of utility asserted and the subject matter claimed."[26]

The Board took a similar approach in another case involving a method of treatment claim, *Ex parte Sudilovsky*.[27] In that case the Board affirmed rejection for failure to demonstrate utility of claims to a method for inhibiting onset of or treating tardive dyskenesia, noting that the record indicated lack of predictability in the art and that the specification did not disclose experimental data or test results.[28]

Two recent developments may signal an end to the trend in the PTO toward increasingly restrictive applications of the utility requirement. First, the PTO has published new Utility Examination Guidelines admonishing examiners that a rejection for lack of utility is inappropriate if the applicant makes an assertion of utility that would be credible to a person of ordinary skill in the field or if the invention has a well-established utility.[29] An accompanying legal analysis prepared by the PTO affirms that inventions asserted to have utility in the treatment of human or animal disorders are subject to the same utility requirement as inventions in other fields of technology, and that "[O]ffice personnel should not construe § 101, under the logic of 'practical' utility or otherwise, to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans. . . . These general principles are equally applicable to situations where an applicant has claimed a process for treating a human or animal disorder."[30] These guidelines grew out of a PTO hearing in October 1994 on intellectual property issues of concern to the biotechnology industry, at which numerous witnesses complained that the PTO had been mishandling the utility requirement and inappropriately

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[26] *Id.*

[27] 21 U.S.P.Q.2d (BNA) 1702 (Bd. Pat. App. & Interf. 1992).

[28] *Id.* at 1705.

[29] PTO Utility Examination Guidelines, 60 Fed. Reg. 36,263 (1995).

[30] *Legal Analysis Supporting Utility Examination Guidelines*, 50 Pat., Trademark & Copyright J. (BNA) 297, 300 (Jul. 20, 1995) [hereinafter *Utility Examination Guidelines*].

demanding from patent applicants the sort of proof of clinical efficacy that the FDA requires prior to approval of a new drug application.[31] In announcing the proposed guidelines at a press conference, PTO Commissioner Bruce Lehman underscored his commitment to implementing the new guidelines through improved training of the examiners and supervisors and, if necessary, through changes in management practices or personnel.[32]

Second, the Court of Appeals for the Federal Circuit very recently reversed a PTO decision rejecting claims to a new pharmaceutical invention for lack of utility in *In re Brana*,[33] chiding the PTO that the issue of what an applicant must prove to establish the utility of such an invention "is one which we would have thought had been settled by case law years ago."[34] The patent claims in that case were directed toward new chemical compounds for use as antitumor substances. The prior art revealed that structurally similar compounds had shown *in vivo* activity against implanted murine lymphocytic leukemias, and the specification reflected greater *in vitro* activity against human tumor cells for the claimed compounds than for the prior art compounds. The examiner concluded that these tests were insufficient to establish the utility of the claimed compounds, and the Board affirmed.

The Federal Circuit reversed, indicating that the utility requirement was more than satisfied in this case. First, the court noted that disclosures of utility in the specification are presumptively correct unless manifestly based on implausible scientific principles, and that "treating cancer with chemical compounds does not suggest an inherently unbelievable

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[31] *See, e.g.*, Biotechnology Industry Organization, *Critical Synergy: The Biotechnology Industry and Intellectual Property Protection*, Presentations of the Intellectual Property Committee of the Biotechnology Industry Organization at the Hearing of the U.S. Patent and Trademark Office (October 17, 1994).

[32] *PTO Announces New Biotechnology Guidelines*, 49 Pat., Trademark and Copyright J. (BNA) 223, 224 (Jan. 5, 1995).

[33] 51 F.3d 1560, 1562, 34 U.S.P.Q.2d (BNA) 1436, 1437 (Fed. Cir. 1995).

[34] *Id.* at 1564, 34 U.S.P.Q.2d (BNA) at 1439.

undertaking or involve implausible scientific principles."[35] The burden was initially on the PTO to provide evidence showing that someone of ordinary skill in the art would reasonably doubt the asserted utility.[36] The PTO had not met this burden, and thus the burden of proof did not shift back to the applicants for rebuttal. However, even if the burden had been shifted, the court was satisfied that the applicants had proferred sufficient rebuttal evidence to establish the utility of the compounds in the form of data showing significant antitumor activity *in vivo* in mouse models.[37] The court dismissed the PTO's argument that *in vivo* tests in animals are not sufficiently predictive of therapeutic efficacy in humans to establish utility with a sharp reminder to the PTO of its limited role in the regulation of pharmaceuticals:

> The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. . . . FDA approval . . . is not a prerequisite for finding a compound useful within the meaning of the patent laws. . . . Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. . . . Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.[38]

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[35] *Id.* at 1566, 34 U.S.P.Q.2d (BNA) at 1441 (citing *In re* Jolles, 628 F.2d 1322, 1327, 206 U.S.P.Q. (BNA) 885, 890 (C.C.P.A. 1980)).

[36] *Id.*

[37] *Id.* at 1567, 34 U.S.P.Q.2d (BNA) at 1441-42.

[38] *Id.* at 1567, 34 U.S.P.Q.2d (BNA) at 1442-43.

The latest word from both the Federal Circuit and the PTO thus suggests that the utility standard for biotechnology inventions may be receding from its recent high-water mark.

Although proof of clinical efficacy may no longer be required to establish patentable utility, it bears emphasis that both the PTO and the Federal Circuit continue to require that, at least in cases where the invention does not have a well-established utility, the utility of a claimed invention be specifically identified in the patent application. Thus in its *Legal Analysis Supporting Utility Examination Guidelines*, the PTO observes that "a statement that a composition has an unspecified 'biological activity' or that does not explain why a composition with that activity is believed to be useful fails to set forth a 'specific assertion of utility.'"[39] And in *In re Brana* the Federal Circuit conceded that the PTO's argument that the application failed to disclose a specific disease that could be treated with the claimed compounds, thereby requiring undue experimentation before the invention could be put to use, was "not without merit."[40] In the end, however, the court was satisfied that comparisons made in the application between the effectiveness of the claimed compounds and prior art compounds implicitly asserted that the claimed compounds were useful against lymphocytic leukemia.

Another recent decision of the Federal Circuit, in a case not involving a pharmaceutical product, affirms that the utility requirement still operates to withhold patent protection from inventions that are too far removed from practical applications.[41] *In re Ziegler* involved an appeal from a rejection of a U.S. patent application claiming priority in the discovery of polypropylene on the basis of a German patent application filed in 1954.[42] The examiner rejected the claims at issue in part on the ground that the German

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[39] *Utility Examination Guidelines, supra* note 30, at 302.

[40] *Brana*, 51 F.3d at 1565, 34 U.S.P.Q.2d (BNA) at 1440.

[41] *In re* Ziegler, 992 F.2d 1197, 26 U.S.P.Q. 2d (BNA) 1600 (Fed. Cir. 1993).

[42] A U.S. patent application filed within one year of a foreign patent application is treated as if it had been filed on the foreign filing date for purposes of determining what counts as prior art, provided the foreign application satisfies the disclosure requirements of U.S. law. 35 U.S.C. § 119 (1994); Kawai v. Metlesics, 480 F.2d 880, 178 U.S.P.Q. (BNA) 158 (C.C.P.A. 1973).

application failed to disclose a practical utility for polypropylene. That application disclosed that polypropylene is "plastic-like" and that it may be pressed into a flexible film with a characteristic infrared spectrum. A previous court in another proceeding had rejected Ziegler's argument that the disclosure that polypropylene is "plastic-like" established its utility, and Ziegler was therefore precluded from relitigating this issue.[43] Thus the only remaining question was whether the disclosure that polypropylene is solid and that it may be pressed into a flexible film with a characteristic infrared spectrum was sufficient to establish a practical utility for the material. In affirming the PTO's determination that it did, the Federal Circuit echoed the concerns over premature filings expressed by the Supreme Court in *Brenner v. Manson*:[44] "We are convinced that, at best, Ziegler was on the way to discovering a practical utility for polypropylene at the time of the filing of the German application; but in that application Ziegler had not yet gotten there."[45] The court concluded: "While we are cognizant of Ziegler's noteworthy contributions to polymer chemistry, we must nevertheless abide by the principle underlying 35 U.S.C. § 101 that a patent 'is not a reward for the search, but compensation for its successful conclusion.'"[46]

Under the standards set by these cases, the inventions claimed in the NIH patent applications may well lack patentable utility, although the issue is not entirely free from doubt. We turn to the specific facts of the Venter applications.

B. *Utility Of The NIH Inventions*

Plainly, these applications were drafted with the possibility of a utility rejection in mind. The specifications are replete with imaginative suggestions for how to use the claimed sequences, individually or in panels, many of which are set forth in prophetic (untested) examples. The specification recites that ESTs may be used as probes to isolate coding sequences and complete genes, which may then be mapped to chromosomal locations. They may be used as chromosome markers. Complete genes,

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[43] *Ziegler*, 992 F.2d at 1201, 26 U.S.P.Q.2d (BNA) at 1604.

[44] 383 U.S. 519, 535, 148 U.S.P.Q. (BNA) 689, 696 (1966).

[45] *Ziegler*, 992 F.2d at 1203, 26 U.S.P.Q.2d (BNA) at 1605.

[46] *Id.* (quoting *Brenner*, 383 U.S. at 536, 148 U.S.P.Q. (BNA) at 696).

isolated through use of the EST probes, may be expressed in recombinant host cells to obtain their protein or polypeptide products. ESTs, or other sequences obtained through the use of ESTs, may be used as diagnostic probes, to detect the presence of a specific mRNA in a particular cell type, or in genetic linkage analysis, or to locate gene regions associated with genetic disease. ESTs may be used to regulate gene expression through triple helix formation or antisense methods. Panels of ESTs may be used for individual identification for forensic and other purposes, a use for which the estimated eighty-five percent of the ESTs that appear to come from noncoding regions are said to be particularly well suited because polymorphisms are more common in noncoding regions. Panels of ESTs specific to particular tissue types may also be used as reagents to identify tissue specimens by organ type or by species.

It is only necessary to show one practical utility for an invention in order to patent it.[47] Thus if any one of the utilities recited in the Venter applications amounts to a practical utility and is supported by an enabling disclosure, the sequences or panels of sequences that are shown in the specification to have this utility will pass the utility test. Moreover, the patent rights that could be obtained on the basis of such a disclosure of practical utility would not be limited to use of the sequences for the disclosed purposes, but would potentially extend to all uses of the sequences.

The patent examiner was unimpressed by the suggested utilities, and rejected the '195 appplication for lack of utility, among other grounds, in an Office Action dated August 20, 1992:

> The mere mention of general possible uses is not sufficient to establish a definite utility because the instant application does not disclose a patentable utility for the oligonucleotides or other nucleotides of the claimed inventions in their currently available form. Given what is disclosed in the instant application, it would be necessary for one to do further work in order to establish a utility for many of the nucleotides embraced by the

[47] 35 U.S.C. § 101 (1994).

> claims. The instant application does not teach one of skill in the art the significance of any putative result of any of the tests or processes alluded to in the application. Although the oligonucleotides embraced by the claims may be hybridized to a variety of different preparations of other nucleic acids, one of skill in the art has no clue as to the significance of any results of such hybridization because the instant application fails to provide any basis for the interpretation of any putative results. Thus, given the invention in its currently available form, others would be compelled to experiment, interpret results, and invent a patentable utility for the claimed nucleotides.

In other words, the recited utilities were inadequate because a skilled person reading the specification would have to engage in further undue experimentation in order to put the claimed inventions to the suggested uses.

As noted above, in order to satisfy the utility requirement, a patent applicant must not only disclose a specific, practical use for the claimed invention but must also provide a disclosure that enables others working in the same field to use the invention in the described manner without having to do more than routine experimentation. Whether this enablement dimension of the utility requirement has been satisfied as to the recited utilities depends on the state of knowledge in the field at the time of filing and the level of skill among ordinary practitioners working in the field.[48] Working examples in the specification may help in satisfying this requirement, particularly if they indicate that the applicant has successfully put the invention to the recited uses. Prophetic examples that describe how to do something the applicants have not yet done in their own laboratories are less probative of enablement, but they may be sufficient if there is no reason to doubt that the instructions are adequate to make the invention

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[48] *In re* Vaeck, 947 F.2d 488, 495-96, 20 U.S.P.Q.2d (BNA) 1438, 1444 (Fed. Cir. 1991); *In re* Sichert, 566 F.2d 1154, 1161, 196 U.S.P.Q. (BNA) 209, 215 (C.C.P.A. 1977).

operable for the described use without undue experimentation.[49] On the other hand, if a person with ordinary skill in the field would question the validity of the applicants' assertions of utility, the burden of proof shifts to the applicants to demonstrate their truth.[50]

Application of these principles is highly specific to the facts of particular cases. The requirement is harder to satisfy without actual data showing success in the laboratory in fields that exhibit greater unpredictability in experimental outcomes. Thus, patent examiners are typically more skeptical of asserted utilities based on prophetic examples for chemical inventions than for mechanical inventions. Examiners have shown particular skepticism toward unproven utilities for drugs and therapeutic inventions, although this attitude may be changing in light of the recent developments discussed above.

Returning to the Venter application with these general principles in mind, the disclosed utilities that are most vulnerable to challenge are those that either (1) do not indicate a specific purpose for which the inventions may be used, or (2) depend for their operability on the success of experiments that have not been performed and are not certain to work in the minds of other practitioners of ordinary skill in the field. The former category would seem to include the claimed utilities as diagnostic probes in genetic linkage analysis, as probes to locate gene regions associated with genetic disease, for regulation of gene expression through antisense and triple helix methods, and for differentiating tissue types. Even if these asserted utilities no longer trigger the heightened skepticism as to operability and enablement recently applied by the PTO to pharmaceutical and therapeutic inventions, they remain vulnerable to challenge on the ground that undue experimentation would be necessary in order to determine which if any diagnostic or therapeutic purposes any of the ESTs might serve. Yet each of these utilities is described in broad, general terms and in purely prophetic examples, unsupported by specific experimental

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[49] *See* Atlas Powder Co. v. E.I. DuPont Nemours, 750 F.2d 1569, 1577, 224 U.S.P.Q. (BNA) 409, 414 (Fed. Cir. 1984); Amgen, Inc. v. Chugai Pharmaceutical Co., 13 U.S.P.Q.2d (BNA) 1737, 1775 (D. Mass. 1989).

[50] *See In re* Brana, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d (BNA) 1436, 1441 (Fed. Cir. 1995); *In re* Bundy, 642 F.2d 430, 433, 209 U.S.P.Q. (BNA) 48, 51 (C.C.P.A. 1981).

data that would identify the significance of any particular sequence to any particular disease.

We lack the technical expertise to evaluate which of the remaining utilities would be met with skepticism by skilled persons in the field or would require undue experimentation to carry out. Uses of the disclosed sequences as probes for diagnosing disease gene regions or to control gene expression through triple helix formation or DNA or RNA antisense molecules seem particularly vulnerable to challenge on this basis. Each of these utilities seems to require a subsequent research effort that appears fraught with uncertainty on the basis of the limited information provided in the specification and the state of the art.

The asserted utility of panels of sequences for tissue typing or for forensic identification purposes may also be vulnerable on this ground. The utility of the sequences in tissue typing depends on the sequences being variably expressed in different types of tissue. The specification states that subtractive hybridization was used to selectively remove sequences shared by a cDNA library from a human lung fibroblast cell line, but it does not indicate which of the remaining sequences is unique to brain tissue. Similarly, the utility of the sequences for forensic identification purposes depends on their being polymorphic. The specification states that eighty-five percent of the sequences appear to come from noncoding regions and that polymorphisms are particularly common in noncoding regions, but it does not indicate which, if any, of the sequences is in fact polymorphic. Perhaps these difficulties can be overcome by using panels that are so large that the likelihood of variable expression by tissue type or polymorphisms across individuals becomes overwhelming. But in that case the asserted utilities would only seem to support the patentability of these large panels, and not of smaller panels or of individual sequences.

A related problem is that the disclosure gives only limited guidance as to which of the sequences (or which combinations of sequences) are suitable for which of these uses. The process of selection may itself involve undue experimentation. As Examiner Martinell stated in reference to the panel claims, "[T]he panel of oligonucleotides in claim 22 has no patentable utility because the instant application fails to disclose a single such panel out of the astronomical number of such panels possible and disclose any use for such a putative panel in its currently available form." Moreover, even if the disclosure is fully enabling as to how to select appropriate sequences or panels, the disclosed utilities will only support the patentability of those

sequences or panels that are useful for those purposes and not the others. To the extent that the disclosed utilities work only for some of the sequences or only for some panels of sequences, the claims are overly broad.

Of all the asserted utilities for the ESTs, the most credibly operable and enabled are the use as probes to obtain full cDNA sequences and the use as chromosome markers. Although only a small handful of cDNAs corresponding to ESTs had actually been fully sequenced as of the filing date, the same procedure could be readily followed by other skilled persons in the field if they were motivated to do so. Similarly, although only a small fraction of the ESTs had actually been mapped to chromosomes as of the filing date, mapping the others according to the methods disclosed in the specification may involve no more than routine experimentation.[51] But these uses may be particularly vulnerable to challenge under *Brenner v. Manson* as representing utility only as an object of study in subsequent research rather than showing "specific benefit . . . in currently available form."

Use of the ESTs as probes to obtain full cDNA sequences has no practical benefit unless and until the full sequences themselves may be used for some purpose beyond research. Subsequent research may well prove some of the genes useful for diagnostic or therapeutic purposes, but the information disclosed in the specification fails to identify which of the genes will be useful, or for which purposes. Practical utility of the sequences awaits determination of the function of the genes they are associated with, thus implicating the concern for premature filing underlying the decisions in *Brenner v. Manson*[52] and *In re Ziegler*.[53]

This concern with premature filing seems particularly on target in this context because it parallels the reactions of scientists to the NIH filings. Scientists quoted in the popular and scientific press repeatedly expressed an

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[51] Examiner Martinell assumed otherwise in his second office action dated August 10, 1993, in which he noted that a DNA sequence covered by the claims may hybridize to more than one chromosome. If this is correct, then the disclosure is inadequate to enable use of the sequences for mapping and the utility of the sequences has not been established on this basis.

[52] 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[53] 992 F.2d 1197, 26 U.S.P.Q.2d (BNA) 1600 (Fed. Cir. 1993).

intuition that NIH was claiming too much in light of the very preliminary information that they had disclosed.[54] It seems likely that the PTO and the courts might have a similar reaction, and that a utility rejection would present an appealing doctrinal basis for expressing that view.

Use of the ESTs as markers presents a closer question. Assuming that the disclosure is sufficiently enabling to allow the sequences to be mapped, the mapped sequences may be useful as markers right away without waiting to learn what genes they come from or the functions of those genes. Such markers are sold commercially, albeit to researchers. Does the existence of a commercial market among researchers confer patentable utility on research reagents? Existing caselaw does not unambiguously resolve this question, and policy arguments could be made on either side of the issue. One could argue that research tools are like the process for making the steroid at issue in *Brenner v. Manson*[55]—merely a means for facilitating subsequent research and not yet offering any "specific benefit . . . in currently available form." Moreover, there are reasons to be wary of patents on research tools, including concerns that they might be licensed on an exclusive basis to the detriment of subsequent research.[56] On the other hand, genetics research is big business, and private firms are playing a growing role in generating tools for the use of genetics researchers in the public and private sectors. Withholding patent protection from research tools could undermine incentives to develop such tools in the private sector and to make them available to researchers. In the absence of patent protection, a public institution such as NIH will presumably place its research tools in the public domain; the same cannot necessarily be expected of the private firms whose sequencing efforts in recent years have far outpaced those of NIH. Under these circumstances, it is not clear whether

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[54] *See e.g.*, Robin Herman, *The Great Gold Rush: U.S. Rankles Other Countries With Preemptive Strike in the Race to Patent Human Genes*, WASHINGTON POST, June 16, 1992, at Z11; Earl Lane, *Debate Over Gene Patent Application; Scientists Argue NIH's Claim Will Choke a Free Flow of Data*, NEWSDAY, May 19, 1992, at 55.

[55] 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[56] For an expanded discussion of this issue focussing on the controversy over these particular patent applications, see Rebecca S. Eisenberg, *Technology Transfer and the Genome Project: Problems with Patenting Research Tools*, 5 RISK: HEALTH, SAFETY & ENV'T 163 (1994).

a strong view of the utility requirement for DNA sequences or other research tools would on balance promote subsequent research or retard it.

In sum, although the utility issues raised by these patent applications have no clear answers, in light of recent caselaw it is not surprising that the PTO rejected the claims of the '195 application for lack of utility, nor would we be surprised to see the Federal Circuit affirm the rejection on this ground. The primary reasons for this reaction are: (1) many of the asserted utilities involve use for vaguely identified diagnostic or therapeutic purposes, with no indication of the particular diagnostic or therapeutic purposes for which any particular sequence or group of sequences might be used; (2) most of the sequences may not be put to the asserted uses without further experimentation which appears to go beyond routine experimentation, and the outcome of which is uncertain; and (3) the utilities that appear least problematic on enablement and operability grounds—use of the sequences as probes for finding full-length cDNAs or as chromosome markers—are most vulnerable to challenge on the ground that they are merely of interest to researchers and don't yet amount to practical utility in currently available form.

IV. NOVELTY

Two fundamental requirements for patent protection are that the invention be new and that it be nonobvious.[57] Both of these requirements were invoked by the examiner in rejecting the '195 and '911 applications.

A. *Background And Applicable Law*

An invention is new if it does not exist in the prior art (i.e., if it has not been disclosed in prior patents or publications and was not known or used by others).[58] The novelty requirement is technical in that the claimed invention must be identically disclosed in a single prior art reference in order to be unpatentable.[59] Thus patent lawyers who have the relevant prior art references before them may often avoid novelty rejections by tinkering with

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[57] 35 U.S.C. §§ 102, 103 (1994).

[58] 35 U.S.C. § 102 (1994).

[59] RCA Corp. v. Applied Digital Data Sys., Inc., 730 F.2d 1440, 221 U.S.P.Q. (BNA) 385 (Fed. Cir.), *cert. dismissed*, 468 U.S. 1228 (1984).

the claim language to avoid covering subject matter that has been disclosed in the prior art.

On the other hand, the novelty standard is at the same time quite exacting, particularly for broadly worded claims, in the following sense: If a prior art reference discloses something that falls within the scope of a claim, the entire claim is invalid, even though much of what the claim covers has not been disclosed in the prior art, and even if the applicant's disclosure makes a significant contribution to the art that was beyond the contemplation of those familiar with the prior art. For example, if a patent is issued with a generic claim covering what is believed to be a new class of chemicals, and it is subsequently discovered that a chemical previously in use by others for an unrelated purpose belongs in that class and is therefore covered by the claim, the claim is invalid in its entirety.

B. *Novelty Of The NIH Inventions*

Because the novelty of a claimed invention is defeated by finding in the prior art a single embodiment falling within the scope of the claim language, it can be treacherous for broadly-worded claims, particularly if the subject matter covered by the claims cannot be readily identified, and the prior art can therefore not be searched effectively. Consider, for example, the August 20, 1992 rejection of the '195 application, which included a rejection for lack of novelty of claims that, as initially drafted, covered portions of the disclosed sequences that were at least fifteen nucleotides in length. Among the prior art references cited by the examiner was a Pharmacia P-L Biochemicals 1984 Product Reference Guide. This catalog listed among the commercial reagents for sale two oligodeoxynucleotides, oligo(dA) and oligo(dT), consisting of chains of repeated A and T nucleotides, respectively. These commercially available sequences were sufficient to defeat the novelty of the original broadly-worded claims because some of the sequences disclosed in the specification included at least one run of fifteen or more A or T nucleotides, and because the claim language was drafted to cover portions of the sequences of at least fifteen nucleotides. NIH responded to this particular rejection by narrowing the claims to cover only fragments of at least 150 nucleotides, but even the amended claims might be subject to a similar challenge.

Those claims that cover undisclosed gene fragments may be particularly vulnerable to challenge on this basis at a later date because there is no way of searching the prior art at present to determine whether it

discloses sequences covered by these claims. For example, claim 17 of the '195 application covers polynucleotide fragments at least 150 base pairs in length from any gene corresponding to any of the disclosed ESTs. Such a fragment could be from a remote region of the gene and have a DNA sequence that is completely dissimilar to anything disclosed in the specification. Since there is no way at present to determine what all of these sequences are, one cannot search the prior art to determine whether the claims are valid. A claim that does not define the invention with sufficient clarity to allow a proper search of the prior art may be invalid for lack of definiteness of the claim language, as discussed more fully below.[60] But even if a patent were to issue on such a claim, the claim could later be challenged on the basis of prior art existing at the time of the filing that becomes salient at a later date when it is realized that one of the ESTs corresponded to a gene that had previously been fully or partially sequenced. If any sequence covered by the claims may be found anywhere in the prior art, any claim covering that sequence would be invalid in its entirety.

While we are not in a position to offer a definitive opinion on the novelty of the claimed sequences, it is worth noting that the examiner also has not conducted an exhaustive search of the sequences embraced by the claims. Instead, the examiner searched the prior art for matches to 15-mer regions from a small number of the disclosed ESTs. The examiner noted that an exhaustive search of all possible 15-mer regions in just the 2,421 sequences disclosed in '911 would have taken until the year 2035 to complete. It is not clear to us why the examiner was unable to search public sequence databases for exact matches to any 15-mer region from any of the disclosed sequences in the time available to him, but given that he did not conduct such a search, it is possible that the prior art includes exact matches to fragments even of the disclosed sequences that did not come to his attention. The potential for overlooking pertinent prior art is magnified when one considers the possibility that undisclosed (and therefore unsearchable) sequences covered by the claims might also exist in the prior art. The broader the claims, the more likely they are to lack novelty.

V. NONOBVIOUSNESS

Whereas the novelty requirement asks whether a claimed invention is identically disclosed in the prior art, the nonobviousness requirement asks

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[60] *See infra* Part VI. C.

whether the invention represents a big enough technical advance to merit a patent.

A. *Background And Applicable Law*

A new and useful invention that someone of ordinary skill in the field would consider obvious in light of the prior art may not be patented.[61] Whether an invention satisfies this standard depends on (1) the scope and content of the prior art; (2) the level of ordinary skill among practitioners in the field of the invention; and (3) the differences between the invention and the prior art.[62] This determination turns on evaluation of technical facts that are beyond our ken. Nonetheless, the Federal Circuit has repeatedly stated that determinations of obviousness are ultimately legal judgments,[63] and so we turn to the relevant case law.

We begin by noting that existing case law leaves some uncertainty as to the proper analytical approach to take in determining the obviousness of a novel DNA sequence. A major source of confusion is a lack of clarity in the cases as to whether the requisite nonobviousness is to be found in the method of obtaining the sequence or in the sequence itself. Section 103 of the Patent Act recites that "[p]atentability shall not be negatived by the manner in which the invention was made."[64] This inartful language is generally understood to mean that an invention may be patentable even if it was arrived at through tedious but routine experimentation rather than through ingenious insight.[65] As long as the end result is nonobvious, the path by which the inventor got there should not defeat patentability. This principle has been particularly important in the chemical arts, where methods for synthesizing new chemicals are often obvious to practitioners of ordinary skill. Such new compounds may be deemed prima facie obvious if they are

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[61] Graham v. John Deere, 383 U.S. 1, 11, 148 U.S.P.Q. (BNA) 459, 464 (1966) (citing Hotchkiss v. Greenwood, 52 U.S. (11 How.) 248 (1851)).

[62] 35 U.S.C. § 103 (1994); id. at 11, 148 U.S.P.Q. (BNA) at 464.

[63] *In re* Deuel, 51 F.3d 1552, 1557, 34 U.S.P.Q.2d (BNA) 1210, 1214 (Fed. Cir. 1995).

[64] 35 U.S.C. § 103 (1994).

[65] *Graham*, 383 U.S. at 15 n.7, 148 U.S.P.Q. (BNA) at 474 n.7.

structurally similar to known compounds, but a patent applicant may nonetheless rebut the case of prima facie obviousness by showing that the compounds possess new and unexpected properties not present or suggested in the prior art.[66] The focus is on the product and its properties rather than on the method of making the product.

On the other hand, some cases have upheld the patentability of obviously desirable products on the basis of evidence that inventive skill was required to figure out how to make them,[67] although arguably if the inventiveness resides in the method of making the product rather than in the product itself only the method should be patentable.

Some early cases addressing the patentability of DNA sequences focussed on the obviousness of the method used to isolate the sequence rather than attempting to address separately the obviousness of the sequence itself. For example, in *Amgen Inc. v. Chugai Pharmaceutical Co.*,[68] a defendant in an infringement action challenged the validity of a patent claiming a purified and isolated DNA sequence encoding human erythropoietin ("EPO") and host cells transformed with such a sequence. The district court rejected this challenge on the basis of its finding that the probing and screening methods used by the inventor to isolate the gene were nonobvious. The Federal Circuit affirmed, but suggested in a footnote that it was not clear whether the analytical approach to this issue taken by the parties and the district court was correct:

> We note that both the district court and the parties have focused on the obviousness of a

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[66] *In re* Dillon, 919 F.2d 688, 691, 16 U.S.P.Q.2d (BNA) 1897, 1900 (Fed. Cir. 1990).

[67] *E.g.*, *In re* Pilkington, 411 F.2d 1345, 162 U.S.P.Q. (BNA) 145 (C.C.P.A. 1969) (applicant who invented a "float glass" process for making sheet glass that was free of imperfections was entitled to claim the product itself in a product-by-process claim and should not be limited to obtaining process claims); Shaw v. E.B. & A.C. Whiting Co., 417 F.2d 1097, 162 U.S.P.Q. (BNA) 580 (2d Cir. 1969) (patent on an artificial filament adapted for use as brush bristles was valid where the means of making such a product was nonobvious), *cert. denied*, 397 U.S. 1076 (1970).

[68] 927 F.2d 1200, 18 U.S.P.Q.2d (BNA) 1016 (Fed. Cir.), *cert. denied sub nom.*, Genetics Inst., Inc. v. Amgen, Inc., 112 S. Ct. 169 (1991).

> process for making the EPO gene, despite the fact that it is products (genes and host cells) that are claimed in the patent, not processes. We have directed our attention accordingly, and do not consider independently whether the products would have been obvious aside from the alleged obviousness of a method of making them.[69]

Two years later, the court appeared to focus more on the structure of a DNA sequence than on the method of obtaining it in reversing a determination of obviousness in the case of *In re Bell*.[70] The claimed inventions in that case were DNA and RNA molecules encoding human insulin-like growth factors I and II ("IGFs"). The Board concluded that prior art disclosing the amino acid sequences for the proteins and a general method for isolating genes for which a portion of the amino acid sequence is known by preparing nucleotide probes was enough to make the entire nucleotide sequence prima facie obvious. The Federal Circuit reversed in an opinion that stressed the unpredictability of the structure of the DNA sequence arising from the degeneracy of the genetic code:

> It may be true that, knowing the structure of the protein, one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene. However, because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein. In the case of IGF, Bell has argued without contradiction that the [amino acid sequences disclosed in the prior art] could be coded for by more than 10^{36} different nucleotide sequences, only a few of which are the human sequences that Bell now claims. Therefore, given the nearly infinite number of

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[69] *Id.* at 1207 n.3, 18 U.S.P.Q.2d (BNA) at 1031 n.3.

[70] 991 F.2d 781, 784, 26 U.S.P.Q.2d (BNA) 1529, 1532 (Fed. Cir. 1993).

> possibilities suggested by the prior art, and the failure of the cited prior art to suggest which of those possibilities is the human sequence, the claimed sequences would not have been obvious.[71]

Although this language suggests a very generous attitude toward the nonobviousness of DNA sequences, the court went on to note several facts present in that case that could limit its precedential value in other cases.

First, the court noted that Bell's sequence claims were narrow:

> Bell does not claim all of the 10^{36} nucleic acids that might potentially code for IGF. Neither does Bell claim all nucleic acids coding for a protein having the biological activity of IGF. Rather, Bell claims only the human nucleic acid sequences coding for IGF. Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences suggested by [the prior art] corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.[72]

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[71] *Id.* at 784, 26 U.S.P.Q.2d (BNA) at 1532. One Board case also arguably takes a structural approach to determining the obviousness of a claimed DNA sequence. Fiddes v. Baird, 30 U.S.P.Q.2d (BNA) 1481 (Bd. Pat. App. & Interf. 1993). In that case, the Board stressed structural differences between the prior art DNA sequence for mammalian and bovine basic fibroblast growth factors (FGFs) and the claimed DNA sequence encoding human basic FGF, rather than processes for obtaining the target genes, in concluding that the claimed sequences were not rendered obvious by the prior art. But that case had somewhat idiosyncratic facts, including that the Board elsewhere had held the prior art patent to be nonenabling, thus making it difficult to generalize from its holding. Moreover, the Board cited the process-focussed nonobviousness holding in *Amgen* in support of its decision, making it unclear whether it was the nonobviousness of the structure of the sequence or the nonobviousness of the method of obtaining the sequence (or both) that provided the basis for the decision.

[72] *Bell*, 991 F.2d at 784, 26 U.S.P.Q.2d (BNA) at 1532.

This left open the possibility that broadly worded claims to a DNA sequence encoding a protein with a known amino acid sequence might be rejected as obvious. The basis for the distinction would be that the prior art might make obvious *a* DNA sequence encoding the protein, but not *the* particular sequence covered by the claim.[73]

Second, in *In re Bell*[74] the Federal Circuit interpreted the prior art cited by the examiner as discouraging or "teaching away from" a successful method for finding the target gene because the disclosed method suggested designing a probe based on an amino acid sequence specified by unique codons. This approach would not have worked for finding the IGF genes, because one of them had only a single amino acid with a unique codon and the other had none. The salience of these facts to the court is inconsistent with its apparent focus earlier in the same opinion on structure rather than on the method of obtaining the gene and suggests that it might have reached a different decision if prior art had been cited that suggested a broader range of probing strategies.

The Board distinguished *In re Bell* on this latter basis in *Ex parte Deuel*.[75] In that case the prior art disclosed a partial amino acid sequence for heparin binding growth factors ("HBGFs") and general cloning methods. In holding that this was sufficient to make the gene prima facie obvious, the Board distinguished *Bell* on the ground that in that case the prior art taught away from a viable process for cloning the gene, while in *Deuel* the applicants did not challenge the examiner's assertion that the probing procedure set forth in the prior art would have allowed isolation of the gene

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[73] The Board distinguished *Bell* in part on this basis in *Ex parte* Movva, 31 U.S.P.Q.2d (BNA) 1027 (Bd. Pat. App. & Interf. 1993). In that case, the Board affirmed rejection of claims to DNA sequences and recombinant DNA molecules encoding swine growth hormone or polypeptides displaying the biological activity of swine growth hormone where the claims were drafted to include degenerate sequences encoding the same protein. "If the reasonable expectation of success found to be lacking in *Bell* can be analogized to the likelihood of hitting the center of the bulls-eye on a dart board, the present reasonable expectation of success would be more akin to merely hitting any spot on the dart board." *Id.* at 1034.

[74] 991 F.2d at 785, 26 U.S.P.Q.2d (BNA) at 1532.

[75] 33 U.S.P.Q.2d (BNA) 1445, 1449 (Bd. Pat. App. & Interf. 1993), *rev'd sub nom; In re* Deuel, 31 F.2d 1552, 34 U.S.P.Q.2d (BNA) 1210 (Fed. Cir. 1995).

without undue experimentation and with a reasonable expectation of success.[76] The Board noted that they "do not lightly dismiss appellants' argument that the examiner has not given sufficient weight to the structure or form of the compound or composition, and has improperly concentrated on the method of making it,"[77] yet, in the end, they did not waver from this process-centered approach.[78]

The Federal Circuit very recently reversed this decision of the Board in an opinion that calls into question both of these possible limitations on the reach of its previous decision in *In re Bell*.[79] First, the court reaffirmed that the obviousness of a DNA sequence is to be determined by reference to its chemical structure rather than by considering the manner of its isolation. The court squarely held that a cDNA sequence was not rendered prima facie obvious by prior art disclosures of a partial amino acid sequence for a protein, plus a general method of isolating a cDNA molecule, if there are no structurally similar DNA molecules in the prior art:

> A prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy

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[76] *Id.*

[77] *Id.*

[78] *See also Ex parte* Tanksley, 26 U.S.P.Q.2d (BNA) 1384 (Bd. Pat. App. & Interf. 1992) (affirming rejection of claims to tomato cDNA clones that included ribulose biphosphate carboxylase ("RuBPC") genes in part on grounds of obviousness, where they were isolated in a manner disclosed in the prior art and the procedures utilized to establish the function of those clones were all well-known in the art, whether or not the exact sequence of any of the clones was identical to the sequence of previously disclosed RuBPC clones); *Ex parte* Movva, 31 U.S.P.Q.2d (BNA) 1027 (Bd. Pat. App. & Interf. 1993) (affirming rejection of claims to DNA sequence and recombinant DNA molecules coding for swine growth hormone based on evidence that, at the time of the invention, one of ordinary skill in the art had ample reason to isolate a DNA sequence encoding swine growth hormone and would have found it obvious to do so using known processes with a reasonable expectation of success).

[79] *In re* Deuel, 51 F.3d 1552, 1559, 34 U.S.P.Q.2d (BNA) 1210, 1215 (Fed. Cir. 1995).

> of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein. No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared. . . . This is so even though one skilled in the art knew that some DNA, albeit not in purified and isolated form, did exist. The [claimed DNA sequences] are specific compounds not suggested by the prior art.[80]

The court stated that the PTO's focus on methods for isolating the claimed DNA sequences was "misplaced because the claims at issue define compounds, not methods,"[81] and cited *In re Bell* for the principle that "the existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs."[82] That the prior art might have been sufficient to motivate those working in the field to prepare an undefined cDNA coding for a known or partially known protein did not make obvious any particular resulting cDNA sequence: "The fact that one can conceive a general process in advance for preparing an *undefined* compound does not mean that a claimed *specific* compound was precisely envisioned and therefore obvious."[83] This language suggests that a DNA sequence must be "precisely envisioned," and not merely readily obtainable, in order to be obvious. Thus the specific cDNA sequences set forth in the patent application were not made obvious by the disclosure of a partial amino acid sequence and general cloning methods.

Second, the court concluded that the prior art did not render obvious the broader generic claims to all DNA sequences encoding HBGFs, although

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[80] *Id.* at 1558-59, 34 U.S.P.Q.2d (BNA) at 1215.

[81] *Id.* at 1559, 34 U.S.P.Q.2d (BNA) at 1215.

[82] *Id.*

[83] *Id.* at 1560, 34 U.S.P.Q.2d (BNA) at 1216.

the court suggested that such broad claims might have been obvious if the full amino acid sequence for the protein had been disclosed in the prior art:

> Such an idea might have been obvious from the *complete* amino acid sequence of the protein, coupled with knowledge of the genetic code, because this information may have enabled a person of ordinary skill in the art to envision the idea of, and, perhaps with the aid of a computer, even identify all members of the claimed genus. The [prior art] reference, however, only discloses a partial amino acid sequence, and thus it appears that, based on the above analysis, the claimed genus would not have been obvious over this prior art disclosure.[84]

The court noted, however, that in the absence of disclosure in the specification of how to obtain any DNA sequences coding for HBGFs other than the specific cDNAs set forth in the application, these broader claims might not be fully supported by an enabling disclosure.[85]

B. *Nonobviousness Of The NIH Inventions*

Turning to the facts of the NIH applications with these cases in mind, we first distinguish between the method used to obtain the sequences and the sequences that were thereby obtained. We note that the '831 application claimed the method used to obtain the sequences as a patentable invention. Because '831 was converted to a Statutory Invention Registration ("SIR") and because the claims of a SIR are not examined for novelty and nonobviousness, the PTO did not pass on the obviousness of the method, and we lack the technical competence to make this determination ourselves. Nonetheless, there is some evidence on the face of the specifications that the methods (described as employing "conventional automated DNA sequencing technology") and materials (commercially available and custom-made cDNA libraries) used to obtain the sequences were substantially

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[84] *Id.*

[85] *Id.*

disclosed in the prior art. Moreover, reactions in the scientific community to news of the NIH patent filings indicate that some scientists at the time viewed the technology used to obtain the sequences as not requiring more than ordinary inventive skill.[86]

On the other hand, perhaps it could be argued that the prior art discouraged or taught away from the approach taken by Venter and his colleagues in the relevant time period. The '195 specification indicates that, contrary to the expectations of the scientific community, the applicants had used cDNA screening and sequencing to discover a large number of heretofore unknown human genes. If the prior art gave reason to doubt that the method used would yield the results obtained, it might be argued that the method was nonobvious, and that the nonobviousness of the method should confer patentability on the results (i.e., the sequences). But even if the method used by Venter and his colleagues was nonobvious as of the '831 filing date, this fact would at most confer patentability on sequences claimed prior to the time that the method was placed in the public domain. Once the method was publicly disclosed, the nonobviousness of any subsequently discovered sequences could not be predicated on the nonobviousness of the method itself, because the method would be in the prior art. Thus the potential significance of the nonobviousness of the Venter methodology in making an affirmative case for patentability is quite limited.

Even if the method used to obtain the sequences is obvious, it does not necessarily follow that the sequences themselves are also obvious. Although the matter is by no means free from doubt, we now think it is more likely than not that the Federal Circuit would focus on the structure of the claimed sequences rather than on the method of obtaining them in assessing their obviousness. The decisions of the Federal Circuit in *In re Bell*[87] and *In re Deuel*[88] suggest that if the prior art does not include structurally similar sequences, the sequences themselves will not be deemed obvious. Under this approach, at the very least those claims that are narrowly drawn to specific, novel sequences with no significant partial homologies to known sequences will probably be considered nonobvious. On the other hand, any

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[86] *See e.g.*, John Casey, *The Gene Kings*, BUSINESSWEEK, May 22, 1995, at 25.

[87] 991 F.2d 781, 26 U.S.P.Q.2d (BNA) 1529 (Fed. Cir. 1993).

[88] 51 F.3d 1552, 1558, 34 U.S.P.Q.2d (BNA) 1210, 1215 (Fed. Cir. 1995).

sequences that have significant partial similarities to known sequences may be considered prima facie obvious if they were obtained through an obvious method and if the prior art sequences were of sufficient interest to motivate the search for other, similar sequences.

Although the Federal Circuit now twice has endorsed this structural approach to determinations of obviousness for DNA sequences of specifically identified genes, it is still not entirely clear that the court would eschew consideration of the obviousness of the method of obtaining sequences in considering the patentability of random partial cDNA sequences of unknown function of the sort claimed in the NIH patent applications. Such an approach would seem to make all novel DNA sequences patentable, however trivial the scientific advance that led to their identification. This position collapses the novelty and nonobviousness requirements for DNA sequences. Moreover, a rigid requirement of structural similarity to a known sequence before a DNA sequence will be considered prima facie obvious seems to ignore the reason why structural similarities have been considered relevant to past determinations of the obviousness of new compounds in favor of rote incantation of the facts on which prior decisions have turned, a dubious basis for deciding new cases involving new facts.

The reason that structural similarity to a compound in the prior art has been considered relevant to prima facie obviousness in past decisions in the chemical field is that the usefulness of a prior art compound is presumed to provide the motivation to search for homologues.[89] With this motivation, it is likely that others working in the field will use known methods to find similar compounds, and only if the compounds obtained from such a search possess surprising properties not present in the prior art will they be nonobvious and therefore patentable.

A superficial analogy to these past cases might seem to call for an inquiry into whether the prior art disclosed sequences that were structurally similar to those found by Venter. But a more reasoned approach instead might ask whether the prior art provided comparable motivation to others working in the field to do what Venter and his colleagues did in 1991. While we have not undertaken a comprehensive review of the technical literature, we note that the 1988 report of the National Research Council on Mapping

[89] *In re* Dillon, 919 F.2d 688, 16 U.S.P.Q.2d (BNA) 1897 (Fed. Cir. 1990).

and Sequencing the Human Genome devotes a couple of pages to analyzing the relative merits of cDNA sequencing versus genomic DNA sequencing, suggesting that there was significant (if, in the view of the authors of that report, misguided) support for focussing the resources of the Human Genome Project initially on sequencing large libraries of cDNAs.[90] It does not necessarily follow that other investigators would be motivated to undertake large-scale partial sequencing of randomly selected cDNA clones of the sort pursued by Venter, as opposed to more focussed searches for particular genes of interest.

But whatever the level of motivation to engage in such sequencing prior to Venter's 1991 disclosure, that disclosure set off a frenzy of cDNA sequencing activity that continues to this day. Under these circumstances it seems reasonable to conclude that, at least since late 1991, the prior art has disclosed enough to motivate others working in the field to find new ESTs through random partial sequencing of clones from cDNA libraries. Therefore, the sequences obtained subsequent to that date by Venter and others through the same general method might be deemed prima facie obvious, even if there are no structurally similar sequences in the prior art, for the same reason that past decisions have held novel chemicals prima facie obvious when the prior art discloses structurally similar compounds: in both cases, the prior art provides motivation to use familiar methods to construct the claimed inventions. We reiterate, however, that the Federal Circuit so far has not taken this approach, and that its decisions in *In re Bell*[91] and *In re Deuel*[92] cast some doubt on its willingness to do so.

It could be argued that finding prima facie obviousness on the basis of the method of sequencing alone violates the statement in section 103 of the Patent Act[93] that "patentability shall not be negatived by the manner in which the invention was made."[94] On the other hand, a finding of prima

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[90] NATIONAL RESEARCH COUNCIL, MAPPING AND SEQUENCING THE HUMAN GENOME (1988).

[91] 991 F.2d 781, 26 U.S.P.Q.2d (BNA) 1529 (Fed. Cir. 1993).

[92] 51 F.3d 1552, 34 U.S.P.Q.2d (BNA) 1210 (Fed. Cir. 1995).

[93] 35 U.S.C. § 103 (1994).

[94] *Id.*

facie obviousness does not necessarily "negative" patentability, but merely shifts to the applicant the burden of showing unexpected properties of the claimed inventions not present or suggested in the prior art. This approach has the benefit of withholding patent protection from newly discovered chemicals until the inventor is in a position to disclose more about them than their structure alone. But perhaps lack of utility is a more appropriate doctrinal basis for rejecting such applications than obviousness.

If prima facie obviousness is established, could NIH sustain its burden of showing unexpected properties for the claimed sequences? Perhaps they could do so with a little more work, but we do not believe that they have done so to date. For the most part all that we know about the disclosed sequences is that they are portions of human genes, which is to be expected of partial sequences obtained from human cDNA. In *Ex parte Anderson*,[95] the Board affirmed an obviousness rejection of claims to a DNA sequence encoding a mature human interleukin-3 ("IL-3") protein having a proline residue at position 8 over prior art disclosing a DNA sequence encoding an IL-3 protein having serine at position 8. The structural similarity gave rise to a prima facie case of obviousness and shifted to the applicants the burden of offering rebuttal evidence showing that the claimed compositions possess unexpected improved properties or properties that the prior art does not have.[96] The Board held that the fact that the claimed IL-3 sequence with proline at position 8 was the dominant allele was not sufficient to overcome the prima facie case of obviousness without an explanation of the practical advantages that come from having possession of the dominant allele.[97] NIH has not even made this much of a showing about the properties of its sequences.

In sum, although the nonobviousness of the claimed sequences is uncertain, on the basis of recent decisions of the Federal Circuit we think it is more likely than not that nonobviousness could be established for those sequences that are not similar to any previously known sequences. If any of the sequences show partial sequence similarity to known sequences, they may be considered prima facie obvious. One could argue that the prior art

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[95] 30 U.S.P.Q.2d (BNA) 1866 (Bd. Pat. App. & Interf. 1993).

[96] *Id.* at 1869.

[97] *Id.* at 1870.

since 1991 has plainly disclosed enough information to motivate those working in the field to apply routine sequencing techniques to obtain partial sequences for randomly selected clones from cDNA libraries, and that all sequences obtained since that date should therefore be deemed prima facie obvious. However, the Federal Circuit has not endorsed this analytical approach, and its most recent decisions suggest a far lower standard of nonobviousness for DNA sequences. If any of the sequences are considered prima facie obvious, it does not appear that NIH has sustained its burden of showing that the sequences possess surprising or unexpected properties.

While recent Federal Circuit decisions suggest that the nonobviousness requirement may be more readily satisfied for ESTs than was previously thought, these decisions also call into question a key argument in favor of patenting ESTs. In the debate over patenting ESTs, some people argued that if ESTs were published without obtaining patent protection, their disclosure would render obvious, and therefore unpatentable, the full-length genes of which they are a part, thereby preventing subsequent researchers and firms who wish to develop commercial products based on such genes from obtaining exclusive rights under a patent.[98] Patents on ESTs, and on the full-length genes that could be obtained by using ESTs as probes, would therefore provide an otherwise unavailable source of exclusive rights to protect the interests of those who develop commercial products related to genes for which ESTs have been publicly disclosed.

This argument hinges on disclosure of partial DNA sequences rendering full-length genes obvious. But if partial or even full amino acid sequences for a protein are not sufficient to make the corresponding DNA sequence obvious, it seems unlikely that a partial DNA sequence would make the full-length DNA sequence obvious. Thus the Federal Circuit's position that the obviousness of a method for obtaining a DNA sequence is irrelevant to the obviousness of the sequence itself is a two-edged sword in the debate over patenting ESTs, serving on one hand to reduce the force of an argument against the patentability of ESTs, while on the other hand undermining arguments for the necessity of obtaining such patents to safeguard the commercial viability of future products.

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[98] *See, e.g.*, Reid Adler, *Genome Research: Fulfilling the Public's Expectations for Knowledge and Commercialization*, 257 SCIENCE 908, 911-12 (1992).

Although we think it is unlikely that disclosure of ESTs will make the corresponding full-length genes obvious and therefore unpatentable, disclosure of full-length genes may well render obvious related genes with similar DNA sequences. We can foresee this issue arising in the near future as the owners of private EST databases take newly discovered genes of interest that are published by others, compare them to the previously undisclosed sequences in their databases, obtain full-length sequences for any ESTs that show similarities to the newly identified genes, and file patent applications on them. If such a strategy is successful, it could give the owners of EST databases the power to fence-in the patent rights of those who have identified new genes of interest by obtaining patents on all related genes. Will these related genes be considered prima facie obvious by virtue of their structural similarity to the publicly disclosed sequences? Certainly the initial disclosure of one member of an interesting gene family would provide motivation to others working in the field to probe available sequence databases for related genes, perhaps with a reasonable expectation of success.[99] Yet structural similarity, rather than motivation and reasonable expectation of success, seems to be the cornerstone of the Federal Circuit's nonobviousness analysis in this area to date.[100] Moreover, some of the more expansive language from *In re Deuel* could be understood as requiring that the prior art allow the structure of the subsequently discovered genes to be "precisely envisioned" before they would be considered obvious, suggesting a rather exacting standard of structural similarity. Resolution of the issue may thus turn on the degree of similarity between the prior art sequences and the related sequences found through use of the EST databases. Those who discover new genes of interest and do not wish to have their patent rights fenced in would be well advised to identify and claim related

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[99] As more sequences are entered in public domain databases that are freely available to the scientific community, the likelihood of success in finding related genes increases, making it more likely that the related genes would be deemed obvious. On the other hand, sequences that could only be obtained through access to a proprietary sequence database that is not generally available to the scientific community might still be considered nonobvious if the database were not included in the prior art.

[100] *See In re* Deuel, 51 F.3d 1552, 1558, 34 U.S.P.Q.2d (BNA) 1210, 1214 (Fed. Cir. 1995). *But cf. In re* Jones, 958 F.2d 347, 349-50, 21 U.S.P.Q.2d (BNA) 1941, 1943 (Fed. Cir. 1992) ("[G]eneralization is to be avoided insofar as specific structures are alleged to be prima facie obvious one from the other.").

sequences, including those sequences that may be partially disclosed in public databases, before they publish their results.

VI. DISCLOSURE

In recent years, the Federal Circuit and the PTO have frequently invoked the disclosure requirements set forth in section 112 of the Patent Act in rejecting or holding invalid patent claims involving DNA sequences.[101] We believe that many of the claims in these applications may be vulnerable to challenge on these grounds, particularly the full gene claims and the panel claims.

Section 112 of the Patent Act provides:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.[102]

The courts and the PTO read the first paragraph of this provision as imposing three distinct requirements: (1) a written description of the invention; (2) an enabling disclosure of how to make and use the invention; and (3) disclosure of the best mode of practicing the invention known to the

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[101] *In re* Deuel, 51 F.3d at 1560, 34 U.S.P.Q.2d (BNA) at 1216; Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1213, 18 U.S.P.Q.2d (BNA) 1016, 1027 (Fed. Cir.) *cert. denied sub nom*, Genetics Inst., Inc. v. Amgen, Inc., 112 S.Ct. 169 (1991).

[102] 35 U.S.C. § 112 (1994).

inventor at the time of filing.[103] The second paragraph further requires that the claim language clearly define the invention.

An inventor who is able to comply with these requirements may obtain a patent covering subject matter that she has not yet actually reduced to practice in the laboratory. Thus the Venter applications claim not only the specific ESTs that had actually been identified and sequenced, but also complementary sequences, allelic variations and portions thereof, full genes corresponding or hybridizing to any of the foregoing sequences, fragments of such full genes, vectors containing any such sequences or genes, panels of ESTS or sequence fragments, and antisense oligonucleotides or triple helix probes capable of blocking expression of the products of the full genes.

The examiner rejected the claims of the '195 application for lack of an enabling disclosure, lack of an adequate written description of the inventions, and indefiniteness of the claim language. We consider each of these issues in turn.

A. *Enablement/Scope*

The requirement of an enabling disclosure of how to make and use the invention is justified as a means of ensuring that the public receives its quid pro quo for the patent monopoly. To the extent that it focuses on disclosure of how to *use* an invention, this requirement overlaps with the utility requirement discussed above.

Enablement is a particularly important limitation on the patentability of prophetic claims to inventions that the applicant has not yet actually reduced to practice. What is required is a disclosure that would allow a person of ordinary skill in the field to reduce the invention to practice without "undue experimentation."[104] What constitutes "undue experimentation" varies from one field to the next.

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[103] Glaxo, Inc. v. Novopharm Ltd., 52 F.3d 1043, 34 U.S.P.Q.2d (BNA) 1565 (Fed. Cir. 1995); Transco Prods., Inc., v. Performance Contracting, Inc., 38 F.3d 551, 32 U.S.P.Q.2d (BNA) 1077 (Fed. Cir. 1994); Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 19 U.S.P.Q.2d (BNA) 1111 (Fed. Cir. 1991).

[104] Fiers v. Revel, 984 F.2d 1164, 25 U.S.P.Q.2d (BNA) 1601 (Fed. Cir. 1993); Cross v. Iizuka, 753 F.2d 1040, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

The enablement requirement should not present a significant barrier to the patenting of DNA sequences that have been fully and accurately set forth in the specification. But some of the claims extend beyond those disclosed sequences to cover other sequences (including full genes operably coding for human gene products) that might ultimately be obtained by using the ESTs as probes. In rejecting the claims of the '195 application for failure to provide an enabling disclosure, the examiner noted that the specification lacked information about the coding regions of the disclosed DNA sequences, and questioned whether the ESTs in fact have coding regions:

> Applicants assert that one of skill in the art can determine coding regions with routine skill and then spend three pages briefly outlining the cloning, selection, sequencing, and sequence analyses and judgments needed to make the determination. These manipulations are more than routine experimentation. . . . Even though the ESTs of the instant application were derived from cDNA, the application fails to establish that each and every expressed sequence has a protein coding region or whether a given EST that has a protein coding region is eventually translated. Some of the RNAs from which the ESTs were derived may not be mRNAs or may be mRNAs that are not translated.

Whether these prophetic claims are enabled by the disclosure is ultimately a technical question that is beyond our expertise. Nonetheless, we note that decisions of the Federal Circuit in biotechnology cases seem to reflect a more generous view than the examiner appears to hold of how much experimentation may be tolerated before a disclosure will be considered nonenabling. For example, in *In re Wands*,[105] the Federal Circuit reversed a rejection of claims to an immunoassay utilizing monoclonal high affinity immunoglobulin M antibodies, even though the antibodies described in the disclosure could not be produced without going through extensive procedures to prepare hybridomas and to screen them for production of the desired antibodies. The court noted that there was a high level of skill in the

[105] 858 F.2d 731, 8 U.S.P.Q.2d (BNA) 1400 (Fed. Cir. 1988).

monoclonal antibody art, that all of the methods needed to practice the invention were well known to those of ordinary skill in the art, that the disclosure provided considerable direction and guidance on how to practice the invention and presented working examples, that the nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibodies with desired characteristics, and that practitioners in this field routinely engage in such screening.

Many decisions of the Board involving claims to DNA sequences coding for proteins of known function and partially known amino acid sequence indicate that techniques for obtaining cDNAs using hybridization probes are well-known in the art.[106] It arguably follows that the use of ESTs as probes to obtain full genes does not involve undue experimentation.

On the other hand, a salient distinction between these prior decisions and the present case is that the Venter applications for the most part do not suggest the use of any particular EST as a probe for finding any particular gene, whereas the disclosures at issue in the prior cases suggested the use of particular probes to find target genes. The work that remains to be done to find a target gene is analogous to searching for a particular individual in a telephone directory that has the names and addresses omitted. Even if we assume that each phone number will lead the caller to someone—an assumption that may or may not have a valid corollary for ESTs—the compilation of information is of limited value in finding any given person, even if that person does in fact have a telephone number in the directory and would pick up the phone if the correct number were dialed. Nor, to our knowledge, is this sort of screening effort routine in the field, in contrast to the effort involved in screening hybridomas to identify producers of desired antibodies that the Federal Circuit concluded did not amount to undue experimentation in *In re Wands*.[107] Therefore, it might be argued that undue experimentation is required to find full genes of interest using the Venter disclosures.

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[106] *See, e.g., Ex parte* Deuel, 33 U.S.P.Q.2d (BNA) 1445 (Bd. Pat. App. & Interf. 1993), *rev'd on other grounds sub nom., In re* Deuel, 51 F.3d 1552, 34 U.S.P.Q.2d (BNA) 1210 (Fed. Cir. 1995); *Ex parte* Movva, 31 U.S.P.Q.2d (BNA) 1027 (Bd. Pat. App. & Interf. 1993).

[107] 858 F.2d 731, 8 U.S.P.Q.2d (BNA) 1400 (Fed. Cir. 1988).

A case involving somewhat analogous facts is *Ex parte Tanksley*[108] in which the Board affirmed the examiner's rejection of claims to tomato cDNA clones on grounds of obviousness and failure to identify distinctly the claimed inventions. The Board went on to note that, in the event of further prosecution, the examiner should consider whether undue experimentation is required to practice the invention given that each of the uses suggested by applicants for their inventions involved, as a preliminary step, the identification of clones of interest, a procedure that the prior art suggested involves significant difficulty. A similar argument could be made with respect to many of the claims in the NIH applications, which cover DNA sequences that may not be put to use without first identifying, through nonroutine experimentation, which of the many sequences are of interest for which possible purposes.

The enabling disclosure requirement also serves as a limitation on the permissible breadth of patent claims, providing a basis for rejecting broad, generic claims for which only a small number of embodiments have been disclosed. A number of decisions have invalidated broad patent claims to DNA sequences on the ground that the disclosure is not as broad as the claims. For example, in *Amgen, Inc. v. Chugai Pharmaceutical*,[109] the Federal Circuit affirmed a lower court decision holding invalid a broad generic claim covering all DNA sequences that will encode any polypeptide having an amino acid sequence sufficiently duplicative of erythropoietin (EPO) to possess the property of increasing production of red blood cells. The basis for the holding was that the broad claim was not adequately enabled by the disclosure in the specification of details for preparing only a few EPO analog genes:

> Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs. . . . Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to

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[108] 26 U.S.P.Q.2d (BNA) 1384, 1388 (Bd. Pat. App. & Interf. 1992).

[109] 927 F.2d 1200, 18 U.S.P.Q.2d (BNA) 1016 (Fed. Cir.), *cert. denied*, 112 S. Ct. 169 (1991).

> what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity.[110]

The Board took a similar approach in *Ex parte Ishizaka,*[111] affirming rejection on grounds of obviousness of claims to DNA sequences encoding glycosylation inhibiting factors ("GIFs") and setting forth as a new ground of rejection failure to provide an enabling disclosure corresponding to the breadth of the claims. The claims purported to cover fragments of the disclosed nucleotide sequences of as few as eighteen to twenty bases which are capable of being used as hybridization probes to obtain additional nucleic acids encoding GIF, as well as "a sequence of nucleotides effectively homologous" to such sequences, defined in the specification to mean at least fifty percent homologous. The Board noted that there was no disclosure in the specification showing that any such small fragments had been or could be so employed by others without undue experimentation[112] and cited *Amgen* in concluding that the broad claims to fragments and homologous sequences were not adequately enabled.[113]

The NIH patent applications contain many claims that are comparable to those held invalid in these decisions, including, in particular,

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[110] *Id.* at 1214, 18 U.S.P.Q.2d (BNA) at 1027-28.

[111] 24 U.S.P.Q.2d (BNA) 1621, 1625-26 (Bd. Pat. App. & Interf. 1992).

[112] *Id.* at 1626.

[113] *Id.*

the full gene claims[114] and the panel claims,[115] and are no better supported in the specification. Indeed, these broad NIH claims may be particularly vulnerable to challenge on this ground because the specifications contain no empirically-tested working examples to support them.

The Federal Circuit stressed the importance of working examples in *In re Vaeck*.[116] In that case the applicant claimed a chimeric gene comprising a gene for an insecticidal protein derived from a *Bacillus* bacterium united with a DNA promoter effective for expressing the *Bacillus* gene in a host cyanobacterium, as well as plasmids containing the chimeric gene and host cyanobacteria expressing the gene. The specification disclosed two particular *Bacillus* species as sources of insecticidal protein and nine genera

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[114] Representative of the full gene claims are claims 4 and 10 of the '195 application. As amended, the language of claim 4 reads as follows:

> An isolated polynucleotide operably coding for a native human polypeptide or protein, which includes a region coding for the same amino acid sequence as a native human coding region corresponding to a sequence designated as one of [the disclosed ESTs].

As amended, the language of claim 10 reads as follows:

> An isolated polynucleotide coding for a human protein or polypeptide, which includes a coding region corresponding to [one of the disclosed ESTs]; or a polynucleotide complementary thereto.

Each of these claims potentially covers a great many sequences, none of which has been set forth in the specification.

[115] Consider, for example, claim 22 of the '195 application, which, as amended, claims:

> A panel of at least 100 isolated polynucleotides having the sequences of [one of the ESTs or a fragment thereof at least 150 base pairs in length].

An astronomical number of such panels could be constructed out of the disclosed sequences, but no such panel is actually disclosed in the specification much less tested to see if it can be used for tissue typing or forensic identification as asserted.

[116] 947 F.2d 488, 495, 20 U.S.P.Q.2d (BNA) 1438, 1444 (Fed. Cir. 1991).

of cyanobacteria as useful hosts, but gave only a single working example detailing the transformation of one strain of cyanobacteria. In affirming the examiner's rejection for lack of enablement of the full breadth of the claims, the Federal Circuit noted that "[t]here is no reasonable correlation between the narrow disclosure in appellants' specification and the broad scope of protection sought in the claims encompassing gene expression in any and all cyanobacteria."[117] More recently, in *In re Goodman*,[118] the Federal Circuit affirmed rejection of broad claims to a method for producing mammalian peptides in plant cells supported by a disclosure of only a single working example involving the expression of gamma-interferon in tobacco plants. The court concluded that the specification did not adequately enable the broad scope of the claims.

Enablement is a peculiarly fact-driven inquiry, and the facts of these cases can certainly be distinguished from the NIH applications. Nonetheless, these and other decisions of the Federal Circuit and the Board suggest a parsimonious attitude toward claim scope for biotechnology patents, restricting claimants to that which they have demonstrated can be done successfully through their own working examples. While the Federal Circuit consistently has affirmed that it is sometimes appropriate to allow generic claims covering more than the particular examples disclosed in the specification even in unpredictable fields,[119] as the number of variations embraced by a claim multiply, the court seems to disapprove of broad patent claims that are supported by only a small number of working examples. This trend does not bode well for broad prophetic claims, such as most of those sought by NIH, that are not supported by any empirically-tested working examples.

B. *Written Description*

A related difficulty in claiming subject matter that goes beyond what the inventor has actually reduced to practice is the written description requirement. The Federal Circuit views this requirement as "separate and distinct" from the enablement requirement: "The purpose of the 'written

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[117] *Id.*

[118] 11 F.3d 1046, 1052, 29 U.S.P.Q.2d (BNA) 2010, 2015 (Fed. Cir. 1993).

[119] *E.g.*, *Vaeck*, 947 F.2d at 496, 20 U.S.P.Q.2d (BNA) at 1445.

description' requirement is broader than to merely explain how to 'make and use;' the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*"[120] In other words, while the purpose of the enablement requirement is to put the public in possession of the invention, the purpose of the written description requirement is to ensure that the inventor was in possession of the invention as of the filing date and is therefore entitled to claim that date as the prima facie date of invention. The written description requirement most commonly presents a problem in cases where an applicant subsequently seeks to claim the benefit of a previous filing date in support of claims that were not included in the application as originally filed,[121] but in *Fiers v. Revel* the Federal Circuit invoked the written description requirement in rejecting prophetic claims to a DNA sequence filed before the inventor had actually obtained the sequence.[122]

Fiers v. Revel was a three-way priority contest among rival foreign claimants to patent rights in the DNA sequence coding for human fibroblast beta-interferon ("β-IF"). Understanding this decision requires a brief digression into arcane rules for determining priority of invention under U.S. patent law. Section 102(g) of the Patent Act calls for determining priority of invention by reference to the competing claimants' respective dates of conception and reduction to practice of the invention, and also "the reasonable diligence of one who was first to conceive and last to reduce to practice." Reduction to practice may be either "actual" (i.e., making a tangible embodiment of the invention in the laboratory) or "constructive" (i.e., filing a patent application that provides an adequate disclosure of the invention). Filing a foreign patent application is sufficient to establish

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[120] Vas-Cath v. Mahurkar, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d (BNA) 1111, 1116 (Fed. Cir. 1991) (emphasis in original).

[121] This may happen when an applicant adds new claims by amendment, or seeks the benefit of the filing date of an earlier-filed foreign or U.S. application for claims of a later-filed application, or, in an interference proceeding, when rival applicants claim patent rights corresponding to an interference count that differs somewhat from the claims they had originally filed.

[122] Fiers v. Revel, 984 F.2d 1164, 1170-71, 25 U.S.P.Q.2d (BNA) 1601, 1606 (Fed. Cir. 1993).

priority as of the foreign filing date so long as the foreign application meets the disclosure requirements of U.S. patent law, but an applicant who seeks to prove a priority date prior to the filing date may not rely on any activities that occurred overseas.[123]

Fiers sought to establish priority by proving that he was first to conceive of the invention and was diligent thereafter up to his British filing date. His British application included a disclosure of the complete DNA sequence for the gene. He claimed that his conception occurred when he disclosed a method for isolating the gene to American scientists who brought his protocol back to the United States. These scientists submitted affidavits stating that the protocol was enabling—i.e., that one of ordinary skill in the field would have been able to follow the protocol to isolate β-IF DNA without undue experimentation. Fiers sought to distinguish the *Amgen* decision on this basis, arguing that, in contrast to the uncertainties attending the method held to be nonenabling in that case (screening a genomic DNA library with fully degenerate probes to find the EPO gene), his own method for finding the β-IF gene could have been easily carried out by one of ordinary skill in the art. The Federal Circuit rejected this narrow reading of *Amgen*,[124] holding that "irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility."[125] In other words, proof that the applicants were in possession of an operative method of obtaining the DNA was not sufficient to establish conception of the DNA itself. Conception only of a process for making the DNA would at most support a subsequent product-by-process claim to the DNA obtained by the disclosed process, and would not support

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[123] 35 U.S.C. §§ 102(g), 104 (1994). The implementing legislation for the North American Free Trade Agreement changed U.S. law to permit inventive activities in Canada and Mexico to be proven in support of a priority claim. North American Free Trade Agreement Implementation Act of 1994, Pub. L. No. 182, 107 Stat. 2057.

[124] *Fiers*, 984 F.2d at 1168, 25 U.S.P.Q.2d (BNA) at 1604.

[125] *Id.* at 1169, 25 U.S.P.Q.2d (BNA) at 1604.

a broader claim to the DNA itself without limitation as to the means by which it is obtained.[126]

The court invoked a similar principle in dismissing Revel's claim to priority on the basis of his earlier-filed Israeli patent application.[127] The Israeli application disclosed a method for isolating a fragment of the DNA coding for β-IF as well as a method for isolating mRNA coding for β-IF, but did not disclose a complete DNA sequence. The Federal Circuit concurred

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[126] A product-by-process claim is a claim to a product defined in the claim language in terms of the method by which it is made. Most decisions hold that such claims are limited in scope to products made by the particular method recited in the claim language and would not cover identical products made by other methods. *See, e.g.*, Atlantic Thermoplastics Co. v. Faytex Corp., 970 F.2d 834, 842, 23 U.S.P.Q.2d (BNA) 1481, 1488 (Fed. Cir. 1992), although, there is some authority for the view that the recited process does not limit the scope of product-by-process claims. *See, e.g.*, Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1583, 18 U.S.P.Q.2d (BNA) 1001, 1016 (Fed. Cir. 1991). Following *Fiers*, NIH submitted new claims 44-55 of '195 in product-by-process form. The Federal Circuit did not clearly indicate that such claims would be patentable in *Fiers*, but merely stated that disclosure of an enabling method for obtaining a gene would *at most* support a claim to the gene in product-by-process form:

> Our statement in *Amgen* that conception may occur, *inter alia*, when one is able to define a chemical by its method of preparation requires that the DNA be claimed by its method of preparation. . . . Before reduction to practice, conception only of a process for making a substance, without a conception of a structural or equivalent definition of that substance, can at most constitute a conception of the substance claimed as a process. Conception of a substance claimed per se without reference to a process requires conception of its structure, name, formula, or definitive chemical or physical properties.

984 F.2d at 1169, 25 U.S.P.Q.2d (BNA) at 1604-05. Even if the NIH disclosures are considered enabling as to the full gene claims, we note that, if those claims are limited to full genes obtained by the recited process, the effective scope of the patent monopoly would be quite narrow, as would the commercial significance of the patents.

[127] *Fiers*, 984 F.2d at 1170-71, 25 U.S.P.Q.2d (BNA) at 1606.

with the finding of the Board that Revel's disclosure was insufficient to satisfy the "written description" requirement of section 112 of the Patent Act,[128] noting that the Board had correctly stated that this provision requires a disclosure that is adequate to convey to others in the same field that the inventor was in possession of the claimed invention as of the filing date:

> An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. Revel's specification does not do that. . . . A bare reference to a DNA with a statement that it can be obtained by reverse transcription is not a description; it does not indicate that Revel was in possession of the DNA. . . . As we stated in *Amgen* and reaffirmed above, such a disclosure just represents a wish, or arguably a plan, for obtaining the DNA. If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity. To paraphrase the Board, one cannot describe what one has not conceived.[129]

This decision potentially presents a major obstacle to the patenting of prophetic claims to DNA sequences that have not yet been set forth in the specifications and would appear to render unpatentable most of the commercially significant claims of the NIH applications. Only those claims that are limited to the disclosed ESTs themselves, and perhaps product-by-process claims to other sequences obtained through the use of those sequences as probes, would appear to satisfy the written description requirement as articulated by the Federal Circuit in *Fiers*.

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[128] *Id.* at 1170, 25 U.S.P.Q.2d (BNA) at 1606.

[129] *Id.* at 1170-71, 25 U.S.P.Q.2d (BNA) at 1606.

We think it is unlikely that the Board will read the *Fiers* decision narrowly. In *Fiddes v. Baird*,[130] the Board cited *Fiers* in a priority contest over inventorship of recombinant DNA molecules encoding fibroblast growth factors ("FGFs"). Baird claimed priority on the basis of an application that set forth the amino acid sequence for bovine pituitary FGF and a theoretical DNA sequence encoding that protein, along with a method for obtaining a cDNA corresponding to the protein, but not the naturally occurring gene encoding the protein. The Board held that this disclosure did not contain a written description for the broad class of mammalian FGFs, and further questioned whether the disclosure was enabling even for Baird's narrower claims to the native gene encoding bovine pituitary FGF.[131]

One could try to distinguish these cases by arguing that the written description requirement, like the enablement requirement, becomes easier to satisfy as the state of knowledge advances in a field. The standard is whether the written description is adequate to convey to other skilled practitioners in the field that the applicant was in possession of the invention at the time of filing. As genetics research has advanced, it may have become increasingly routine to use a probe to find a gene, such that by the time of the NIH filings other practitioners might have regarded someone who had found an EST as being for all practical purposes in possession of the corresponding full-length gene.

One problem with this line of argument is that it seems to overlook the distinction that the Federal Circuit has consistently maintained between the enablement and written description requirements. Indeed, in *Fiers v. Revel*[132] the court rejected the priority claims of both Fiers and Revel without challenging their assertions that their disclosures were enabling.

The message that emerges from these decisions is that the patentability of a DNA sequence is doubtful until one can set forth the actual sequence. Unless the Federal Circuit and PTO retreat from this position, it is unlikely that an applicant could claim a full-length gene by disclosing nothing more than a partial sequence and a probing methodology. The

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[130] 30 U.S.P.Q.2d (BNA) 1481, 1483 (Bd. Pat. App. & Interf. 1993).

[131] *Id.*

[132] 984 F.2d at 1171, 25 U.S.P.Q.2d (BNA) at 1605-06.

written description requirement, as recently construed in cases involving claims to DNA sequences, appears to be an insurmountable hurdle for all of the claims in the NIH applications that go beyond the sequences actually set forth in the specification. Even a fully enabling disclosure of how to use a probe to find a full-length gene will not be sufficient to support a claim to the full-length gene, except perhaps in narrow, product-by-process form. In that case, as a practical matter, it may be that the allowable claims could not confer a commercially effective monopoly in anything more than the ESTs themselves.

C. *Definiteness*

A further difficulty for some of the claims is the requirement that the claim language "particularly [point] out and distinctly [claim] the subject matter which the applicant regards as his invention."[133] The purpose of the requirement for definite claim language is twofold: (1) to allow proper examination for patentability; and (2) to give notice to the public of what constitutes infringement.[134] This requirement is likely to be particularly problematic for claims to sequences that have not been identified in the specification. In *Ex parte Tanksley,*[135] the Board affirmed the examiner's rejection of claims to selected tomato cDNA clones that had not been sequenced and, for the most part, had not been identified by biological function, on the ground that the clones had not been adequately described to allow either proper examination in comparison to the prior art or adequate notice to the public of what the claims cover.

We have already noted in the discussion of novelty above that many of the claims cover sequences that are not set forth in the specification and that may not even include sequences set forth in the specification. Thus, for example, claim 17 of '195 covers any polynucleotide fragment of at least 150 base pairs from any gene corresponding to any of the disclosed ESTs. There is no way that an examiner can effectively search the prior art to see if it includes any sequences covered by this claim. Nor does the claim language give notice to the public of the scope of its coverage. Both of the policy

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[133] 35 U.S.C. § 112 (1994).

[134] Graver Tank & Mfg. v. Linde Air Prod. Co., 336 U.S. 271, 277, 80 U.S.P.Q. (BNA) 451, 453 (1949).

[135] 26 U.S.P.Q.2d (BNA) 1384, 1386 (Bd. Pat. App. & Interf. 1992).

interests behind the requirement for clear and definite claim language are thus squarely implicated by the facts of this case.

In sum, the requirements of an enabling disclosure, written description of the invention, and definiteness of claim language appear not to be satisfied for many of the claims of these patent applications, particularly those claims that cover sequences and panels of sequences that are not set forth in the specification. While we lack the technical expertise to offer a definitive opinion on the question of enablement, the absence of working examples and the apparent need for nonroutine screening in order to identify which sequences or panels are suitable for which purposes, suggest that the claims may be vulnerable to challenge on enablement grounds. Moreover, the breadth of some of the claims appears to exceed the scope of enablement under the standards of recent Federal Circuit and Board decisions, particularly in light of the absence of empirically-tested working examples. Claims directed to sequences that are not set forth in the specification also appear to lack an adequate written description as that requirement was articulated for DNA sequences by the Federal Circuit in *Fiers v. Revel*.[136] The absence of sequence information supporting these claims also makes the scope of the claims indefinite, in violation of the statutory requirement that the claims "particularly [point] out and distinctly [claim]" the subject matter of the invention.[137] Those claims that are limited to the sequences that have actually been identified and set forth in the specification are not vulnerable to these challenges.

VII. CONCLUSION

We believe that most of the claims set forth in the NIH patent applications probably are not patentable. Although the matter is not entirely free from doubt, we believe that it is more likely than not that the Federal Circuit would hold all of the claims invalid for lack of utility. The asserted utilities that appear most likely to satisfy the "practical utility" standard of *Brenner v. Manson*[138] either involve vaguely defined medical or therapeutic uses, with no indication in the specification of which sequences will serve

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[136] 984 F.2d at 1172, 25 U.S.P.Q.2d (BNA) at 1607.

[137] 35 U.S.C. § 112 (1994).

[138] 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

which diagnostic or therapeutic purposes, or else would require further non-routine experimentation to carry out. Those utilities that are most credibly enabled on the face of the specification, such as use of the ESTs as markers or probes, are most vulnerable to the challenge that they do not amount to practical utility in currently available form.

The claims that cover sequences and panels of sequences that have not been specifically set forth in the applications are vulnerable to challenge on a number of further grounds. Particularly significant in light of recent caselaw is that they are not supported by an adequate written decision. They may also lack an enabling disclosure or be overly broad relative to the scope of disclosure. Because they cannot be effectively compared to the prior art and do not give clear notice of what they cover, they may be challenged as lacking the requisite clarity and definiteness of claim language. Moreover, it is impossible to determine whether they satisfy the novelty standard.

We are uncertain on the basis of existing caselaw whether any of the sequences satisfy the nonobviousness requirement. Most likely to be vulnerable to a rejection for obviousness are those sequences that are similar to sequences disclosed in the prior art and were obtained through a method that was disclosed or suggested in the prior art. Such sequences might be considered prima facie obvious, in which case it would be necessary to show that they have surprising properties not shared by the prior art sequences in order to establish their patentability. On the other hand, in cases where there are no similar sequences in the prior art, recent Federal Circuit decisions suggest that this approach improperly conflates the method of identifying the sequences with the sequences themselves. Because they are most likely to satisfy the requirements of enablement, written description, and particularity of claim language, the claims that are most likely to be patentable are those that are limited to the actual ESTs disclosed in the patent applications. Patent rights that are limited to such claims are unlikely to be an effective vehicle for technology transfer, however. The primary value of such sequences is in their use as research tools, a use that is unlikely to be inhibited by the absence of patent rights. Indeed, the use of ESTs as research tools might be more attractive to researchers and institutions who are assured that NIH does not and will not claim patent rights to subsequent discoveries that might be facilitated by access to the sequences.