Buffalo Intellectual Property Law Journal

Volume 1 | Number 1 Article 4

7-1-2001

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Scott D. Locke & David A. Kalow, *Preparing for Bioinformatics Litigation: How Will the Courts Confront the Next Generation of Biotechnology Patents?*, 1 Buff. Intell. Prop. L.J. 76 (2001).
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PREPARING FOR BIOINFORMATICS LITIGATION: HOW WILL THE COURTS CONFRONT THE NEXT GENERATION OF BIOTECHNOLOGY PATENTS?†

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INTRODUCTION

Society will likely view the past decade as the birth of the Internet Age. The next ten years, however, will be seen as the golden age of biotechnology. With the advances that will soon occur in genetic technology, scientists will work on projects that once would have sounded like science fiction, and entrepreneurs will appear out of the woodwork in order to try to amass their fortunes.[1] Part of these entrepreneurs' strategies will involve procuring patents. Where there is a patent, there is a potential for patent litigation.

Biotechnology patent litigation has always been complex. It is about to become even more complicated. Biotechnology is increasingly becoming dominated by genetic technology and intertwined with information systems and vast sources of data. This is causing a boom in fields such as bioinformatics, which typically focuses on "sequence-based extraction of specific patterns or motifs and also on specific pat-

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† This article is an updated version of an article that was first presented at the IBC USA Conferences Annual Symposium on Pharmacogenomics, SNPs & Genetic Patenting, May 31– June 2, 2000. That article was entitled *When the Human Genome Project and State Street Collide: Preparing for the Next Generation of Biotechnology Patent Litigation.*

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[1] *The Human Genome Project: Benefiting All Humanity*, ¶21, March 14, 2000, The White House Office of the Press Secretary ("The potential for commercial development of genomics research also presents U.S. industry with a wealth of opportunities, and sales of DNA-based products and technologies in the biotechnology industry are expected to exceed $45 billion by 2009.").

tern matching."[2] Players with foresight have begun and will continue to seek not only the predictable biotechnology patent claims to compositions and methods of diagnosis and treatments, but also claims to processing of information. These processing of information claims should and will likely more resemble software and business method patents than traditional biotechnology patents. This may help to satisfy the demanding requirements of 35 U.S.C. § 112, as they have been applied to what have been viewed as the relatively unpredictable genetic/biotechnology patents, and to provide courts with the opportunity for upholding more patents. It may also allow courts to focus on the policy of broad inclusion of what is patentable, as described in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*,[3] when defendants raise their inevitable challenges to utility and patentability.

The occurrence of three events in the past few years set the groundwork for the next generation of biotechnology patents to issue—the bioinformatics patents,[4] which will provide the subject matter for this next generation of biotechnology patent litigation. First, in 1997, the United States Patent and Trademark Office announced that it would allow claims on expressed sequence tags ("ESTs") based on their utility as probes.[5] This sparked the increase in the filing of genetic-related applications.[6]

Second, in 1998, the Court of Appeals for the Federal Circuit handed down *State Street.*[7] In *State Street,* the court clearly stated that tangible applications of mathematical algorithms and business meth-

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[2] Aris Persidis, *Data Mining in Biotechnology,* 18 NATURE BIOTECHNOLOGY 237 (2000).

[3] 149 F.3d 1368 (Fed. Cir. 1998), *cert. denied*, 525 U.S. 1093 (1999).

[4] Patents in this field have already begun to issue. *See, e.g.,* U.S. Pat. No. 6,141,657, Method and Apparatus for Identifying Classifying or Quantifying DNA Sequences in a Sample Without Sequencing, issued October 31, 2000, assigned to Curagen Corp.; U.S. Pat. No. 6,125,383, Research System Using Multi-platform Object Oriented Program Language for Providing Objects at Runtime for Creating and Manipulating Biological or Chemical Data, issued September 26, 2000, assigned to Netgenics Corp.; U.S. Pat. No. 6,023,659, Database System Employing Protein Function Hierarchies for Viewing Biomolecular Sequence Data, issued February 8, 2000, assigned to Incyte Pharmaceuticals, Inc.; U.S. Pat. No. 5,970,500, Database and System for Determining, Storing and Displaying Gene Locus Information, issued October 19, 1999, assigned to Incyte Pharmaceuticals, Inc.; U.S. Pat. No. 5,966,712, Database and System for Storing, Comparing and Displaying Genomic Information, issued October 12, 1997, assigned to Incyte Pharmaceuticals, Inc.

[5] Dorothy R. Auth, *Are ESTs Patentable*? 15 NATURE BIOTECHNOLOGY 911 (1997); *see also "SNPs" Are Next Focus of Intellectual Property Debate Among Researchers,* 60 THE PINK SHEET 20 (1998) ("The Patent & Trademark Office has since ruled that gene fragments or expressed sequence tags, can be patented for diagnostic purposes.").

[6] These patents and other DNA-related patents have provided the subject matter for the developing body of "genetic/biotechnology" case law.

[7] 149 F.3d 1368.

ods, as well as data processing and computer programs, were patentable. At first blush one may not see the relevance to biotechnology. But as databases that contain programs that manipulate genetic information grow, so too will the methods by which people use them. Biotechnology entrepreneurs with foresight will draft patent applications directed both to the data and to their uses.[8]

Third, the first stage of the Human Genome Project has been completed.[9] This has put a significant amount of information in the scientific community and will provide countless opportunities for biotechnology entrepreneurs. Attempting to encourage the introduction of this information into the public sphere, President Clinton and Prime Minister Blair issued a joint statement recommending that "raw fundamental data on the human genome, including the human DNA sequence and its variations, should be made freely available to scientists everywhere."[10]

With these three events having occurred, now is the time for the genetic/biotechnology industry to plan actively how to craft its patents for maximum protection. In order to do this, the industry must understand how the courts have approached biotechnology patents in general and be prepared for how the courts will approach bioinformatics patents. Below are (I) a survey of the unique areas of genetic/biotechnology case law of which all genetic/biotechnology patent litigants should be aware, (II) an explanation of *State Street* and its importance to the biotechnology industry, and (III) predictions for the future.

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[8] Patents are not the only means for protecting one's intellectual property. For example, databases, which are important in the field of bioinformatics, are protectable under copyright law to the extent that they are original compilations. 17 U.S.C. § 101. However, the protection does not extend to the underlying data. Feist Publications, Inc. v. Rural Telephone Service Co., 499 U.S. 340, 350 (1991); Matthew Bender & Co. v. West Publishing Co., 158 F.3d 693, 699 (2d Cir. 1998), *cert. denied,* 526 U.S. 1154 (1999). Additionally, one should note that foreign nations including those of the European Union have explored other means for protecting databases.

Persons who work in the world of bioinformatics should be aware that some degree of protection is available for databases through the anti-circumvention provisions of the Digital Millennium Copyright Act if the database contains a "technological measure that effectively controls access to a work protected under [Title 17 of the U.S. Code]." 17 U.S.C. § 1201. Thus, even though copyright protection does not extend to the underlying data in a database, it does extend to the selection and arrangement of those data, thereby bringing most databases within the protection of the Digital Millennium Copyright Act and affording them the same protections under that provision as all other copyrighted works. 65 Fed. Reg. 64556, 64566.

[9] *President Clinton Announces the Completion of the First Survey of the Entire Human Genome*, The White House, Office of the Press Secretary, June 25, 2000.

[10] *Joint Statement by President Clinton and Prime Minister Tony Blair of the U.K.*, The White House Office of the Press Secretary, March 14, 2000.

I.
GENETIC/BIOTECHNOLOGY CASE LAW

A patent litigation can be thought of as containing five major components: (1) claim construction, (2) validity, (3) infringement, (4) damages, and (5) counterclaims and affirmative defenses.[11] Each of these subjects merits a separate discussion; however, only the second will be addressed in this article.[12]

A patent may be declared invalid on a number of grounds; the four most important ones for genetic/biotechnology litigants are obviousness, inventorship, enablement, and written description. Thus far, the courts have been focusing on patents for, and related to, DNA and protein sequences; bioinformatics patents have not yet made their way to the courts. But when they do, the courts will be likely to use the cases described below as a starting point.[13]

A. Obviousness

Under 35 U.S.C. § 103, a patent is invalid if it is obvious in light of the prior art. "The foundational facts for the prima facie case of obviousness are: (1) the scope and content of the prior art; (2) the difference between the prior art and the claimed invention; and (3) the level of ordinary skill in the art."[14] From a scientist's point of view,

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[11] Courts typically phrase their analyses as two-pronged: (i) construction of the claims, and (ii) comparison of the claims to the accused product. Gentry Gallery, Inc. v. Berkline Corp., 134 F.3d 1473, 1476 (Fed. Cir. 1998). However, when preparing for a case, the authors believe that this five-part analysis is more practical.

[12] Before addressing the specific issues unique to genetic/biotechnology case law, one should consider a number of issues that must be kept in mind in any litigation. First, litigation is about telling a true story persuasively. Regardless of how good the facts may be, if one cannot convey them to a judge or a jury, one will have difficulties. This requires a litigant to review the facts both as persons remember them and as they appear in documents. It also requires the finding of and working with experts who are credible and presentable to the judge and jury.

Second, litigation involves time and money. The process can take years and will tap both monetary and person-hour resources.

Third, litigation involves discovery, which includes disclosure of documents, including electronic documents and depositions. Someone will review old documents, lab notebooks, and electronic files. Once the litigation has started, little can be done about the content of the documents. Thus, when one writes anything, regardless of whether there is litigation pending, one should remember that one's employer, its lawyers, and its adversaries may someday read it.

[13] The case law discussed herein includes cases between litigants in federal courts, as well as Interference proceedings and *ex parte* proceedings within, and appealed from, the Patent and Trademark Office.

[14] In re Mayne, 104 F.3d 1339, 1341 (Fed. Cir. 1997) (invalidity found for patent relating to proteins). A court may also consider secondary considerations, if any, of nonobviousness. Boehringer Animal Health, Inc. v. Schering-Plough Corp., 984 F. Supp. 239, 254 (D.N.J. 1997). These considerations may include evidence of commercial success of the

under this standard, the DNA sequence of a gene in many circumstances may appear to be obvious.[15] This reaction is often due to the degeneracy of the genetic code; there are only a finite number of possibilities for the sequence of a gene once the protein sequence is known. Thus, once a protein sequence is known, its DNA sequence might require work to find (including finding the gene), but it is generally knowable.

The Federal Circuit, however, has been more generous than one unfamiliar with the patent laws might have predicted,[16] and patents for DNA sequences have been and will continue to be awarded.[17] A claim to a specific DNA sequence is not made obvious by mere knowledge of a desired protein sequence in combination with methods for generating the DNA that encodes that protein.[18] In *In re Bell*, the first of the two seminal Federal Circuit cases addressing the obviousness requirement as applied to genetic/biotechnology patents, the Federal Circuit explicitly rejected the proposition that "the established relationship in the genetic code between a nucleic acid and the protein it encodes also makes a gene *prima facie* obvious over its correspondent protein."[19]

In *In re Deuel*,[20] the second of the two seminal cases on obviousness and genetic/biotechnology technology, the applicants' invention related "to isolated and purified DNA and cDNA molecules that encoded heparin-binding growth factors ('HBGF')."[21] The applicants decoded HBGF from bovine uterine tissue and human placental tis-

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invention, satisfying a long-felt need, failure of others to find a solution to the problem, and copying of the invention by others. *Id.*

15 Scientists who want to procure patents should be cautioned not to put these thoughts in writing.

16 Sara Dastgheib-Vinarov, *A Higher Nonobviousness Standard for Gene Patents: Protecting Biomedical Research from the Big Chill*, 4 MARQ. INTELL. PROP. L. REV. 143, 152-53 (2000) (in biotechnology industry, non-obviousness hurdle has become easy to overcome).

17 *See U.S. Patent Policy Unaffected by US/UK Statement on Human Gene Sequence Data,* U.S.P.T.O. Press Release #00-17, March 16, 2000.

18 *In re* Deuel, 51 F.3d 1552, 1558-59 (Fed. Cir. 1995) ("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 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."). *Deuel* is not without its critics. *See e.g.,* Sara Dastgheib-Vinarov, 4 MARQ. INTELL. PROP. L. REV. at 154; John Murray, *Owning Genes: Disputes Involving DNA Sequence Patents,* 75 CHI.-KENT. L. REV. 231, 247 (1999).

19 *In re* Bell, 991 F.2d 781, 784 (Fed. Cir. 1993).

20 51 F.3d 1552. *In re* Deuel was not a litigation, but instead an appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interference.

21 *Id.* at 1554.

sue.[22] One prior art reference disclosed "a group of protein growth factors designated as heparin-binding brain mitogens."[23] A second prior art reference disclosed a method for isolating DNA and cDNA.[24]

The Federal Circuit took the opportunity to clarify its position that knowledge of a protein sequence does not necessarily render a DNA sequence obvious and "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."[25] It then held that the cDNA molecules that were claimed were not obvious in light of the prior art.[26] Realizing the breadth of its decision, the court also noted: "This is not to say that a gene is never rendered obvious when the amino acid sequence of its coded protein is known . . . [e.g., when] a known amino acid sequence is specified exclusively by unique codons, the gene might . . . [be] obvious."[27] This is consistent with the general rule that an invention that is only "obvious to try" is not unpatentable.[28]

Although in 1993, in *In re Bell*, the Federal Circuit announced clearly that it believed that DNA sequences may be patentable, the Board of Patent Appeals and Interferences provided an example of when a DNA sequence would be obvious in light of a known protein sequence. In *Ex parte Movva*,[29] the Board noted two factors that suggested and supported a finding that a prior art rejection based on a probing DNA library was appropriate. First, the gene of interest was part of the family of mammalian genes, and at least three of those mammalian genes showed highly conserved regions.[30] Second, "the prior art had successfully isolated similar genes of interest using probes based upon one of these known nucleotide sequences."[31]

Ex parte Movva is not prominently cited in the literature or case law. But as more sequences enter the public sphere, each new sequence has a greater chance of being easier to predict in light of what

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22 *Id.* at 1555.

23 *Id.* at 1556.

24 *Id.*

25 *Id.* at 1559.

26 *Id.* at 1560.

27 In re Bell, 991 F.2d at 784. The Federal Circuit continued: "We express no opinion concerning the reverse proposition, that knowledge of the structure of a DNA, *e.g.*, a cDNA, might make a coded protein obvious." *Id.* at 784 n.6.

28 *See* In re Deuel, 51 F.3d at 1559; Boehringer, 984 F. Supp. at 256.

29 31 U.S.P.Q. 2d 1027 (Bd. Pt. App. & Int. 1993).

30 *Id.* at 1030.

31 *Id.*

is known. Thus, potential applicants should continue to file applications for DNA and DNA-related patents, and defendants should always assert that patents for sequences are obvious.[32] Soon, the defendants may prevail.

B. Inventorship

In order for there to be an invention, there must be conception. In terms of patent law, conception requires that an inventor "had a definite and permanent idea of the complete and operative invention" and that "the inventor's idea, as defined and preserved, enables one of ordinary skill in the art to reduce the invention to practice."[33] The inventor must have "both the idea of the invention's structure and possession of an operative method of making it."[34] An inventor's subjective belief that her or his invention will work is irrelevant.[35]

The notion of conception is important for two reasons. First, an inventor must have conceived of the invention prior to filing the application. Failure to have done so is grounds for invalidity. Second, because, under U.S. Patent Law, priority is given to the first to invent and not the first to file, it is important to determine when an invention is conceived.[36] As genetic/biotechnology becomes a more and more lucrative endeavor, increasing numbers of persons will enter the field. This in turn will increase the number of inventions and the rate at which inventions will be discovered, which in turn will increase the number of disputes over who first invented a particular invention.

The Federal Circuit first confronted the issue of what it means to have conception of a gene in *Amgen v. Chugai*.[37] There, the court, drawing support from the application of the law of conception to chemical compounds, held: "A gene is a chemical compound, albeit a

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[32] *See also* Ex parte Goldgaber, 41 U.S.P.Q. 2d 1172 (Bd. Pt. App. & Int. 1996) (DNA sequence was obvious).

[33] Burroughs Wellcome Co. v. Barr Laboratories, Inc., 40 F.3d 1223, 1227 (Fed. Cir. 1994), *cert. denied,* 515 U.S. 1130 (1995). *See also,* Hybritech Inc. v. Monoclonal Antibodies, 802 F.2d 1367, 1376 (Fed. Cir. 1986) (quoting 1 Robinson on Patents 532 (1890): Conception is the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice."), *cert. denied,* 480 U.S. 947 (1987).

[34] Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 927 F.2d 1200, 1206 (Fed. Cir. 1991), *cert. denied sub nom.,* Genetics Inst. v. Amgen, 502 U.S. 856 (1991).

[35] Burroughs Wellcome, 40 F.3d at 1554.

[36] 35 U.S.C. § 102(g). Applicants should note that in many foreign countries, the inquiry focuses on who is the first to file, not the first to invent. Therefore, inventors should not unnecessarily delay filing applications. Peter A. Jackman, *Adoption of a First-To-File Patent System: A Proposal,* 26 U. BALT. L. REV. 67, 73 (1997) ("In contrast with the United States, nearly every other country in the world utilizes a first to file system of priority.").

[37] 927 F.2d 1200.

complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe [how to obtain] it."[38]

One of the claims was directed to a "purified and isolated DNA sequence"; however, the inventors had only an idea as to a general approach for screening a DNA library that might be used to identify and to clone the gene.[39] They did not know its sequence. The court emphasized: "[W]hen an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the gene has been isolated."[40] Thus, an applicant should not prematurely file an application claiming nucleotide sequences. However, an applicant should consider filing method claims even before identifying the exact DNA sequence. There are procedures such as continuation-in-part applications to claim the sequence when it is discovered.

The Federal Circuit revisited the issue of conception with respect to genes two years later in *Fiers v. Revel*,[41] where, in the context of an Interference proceeding, the court reaffirmed the holding of *Amgen,* again noting that conception of a DNA sequence cannot be by its functional utility.[42] The court reemphasized that the existence of a workable method for preparing DNA does not establish conception of that material.[43]

Under U.S. Patent Law, one is concerned with not only conception, but also reduction to practice. For a number of years, according to some courts, inventions that cover biological substances were viewed as not having been conceived prior to their reduction to practice.[44] However, as the Federal Circuit has become more comfortable

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38 *Id.* at 1206.

39 *Id.* at 1206-1207.

40 *Id.* at 1206.

41 984 F.2d 1164 (Fed. Cir. 1993).

42 *Id.* at 1169.

43 *Id. See also,* Schendel v. Curtis, 83 F.3d 1399, 1404 (Fed. Cir. 1996) ("[W]ithout any molecular weight or other probative data relevant to the composition or structure of the molecule [the applicant] allegedly prepared, there is insufficient evidentiary support for Schendel's conclusory assertion that he made an IL-3/G-CSF fusion protein."). The Federal Circuit has noted that other than identifying a sequence, conception may occur when one is able to define a chemical by its "method of preparation" if the DNA is claimed by its method of preparation. Fiers, 984 F.2d at 1171. Thus, conception of a substance *per se,* claimed without reference to a process, requires conception of its structure, name, formula, or definitive chemical or physical properties. *Id.*

44 Brown v. Regents of University of California, 866 F. Supp. 439, 442-443 (N.D. Cal. 1994); Regents of University of California v. Synbiotics Corp., 849 F. Supp. 740, 742 (S.D.

with genetic/biotechnology, this may have begun to change. For a naturally occurring gene sequence, or an EST or SNP (single nucleotide polymorphism), there may be no conception without a simultaneous reduction to practice,[45] but for DNA constructs, such as probes with defined functional regions, conception and reduction to practice may, as they are in the context of most inventions, be distinct events.

Recently, in *Singh v. Brake*,[46] another appeal from the Board of Patent Appeals and Interferences, the Federal Circuit addressed the issue of inventorship in the context of an invention of a DNA construct comprising a DNA encoding alpha factor leading sequence, a spacer, and a gene foreign to yeast.[47] In September and October of 1982, when Singh, one of the parties to an Interference, was working on his idea, he learned that eight additional amino acids were being produced in the translated product, and he needed to develop a means to remove these additional amino acids. Singh alleged that he conceived of the invention on approximately October 1, 1982, when he first learned of this problem and when, according to him, he thought of a solution using "loop deletion mutagenesis." He asserted that evidence in his lab notebooks from November and December supported that he had conceived of the invention prior to January 1983. Singh filed his patent application on June 20, 1983. Brake, the other party to the Interference, filed a patent application on January 12, 1983.

The two main pieces of evidence were documents in Singh's laboratory notebook: (a) an articulation of the problem on November 24, 1982; and (b) Singh's ordering of Synthetic DNA Request for a particular oligonucleotide sequence to incorporate into the construct, with a notation explaining the intended use.[48] Two issues surrounded this evidence. First, there was an issue as to whether the second piece of evidence could be used to corroborate the conception under a theory that the sequence had no other substantial use than to accomplish

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Cal. 1994) (conception did not occur because the inventor had neither isolated the virus at issue nor reduced the concept to practice).

[45] *See* Synbiotics, 849 F. Supp. at 742; *see also,* Brown, 866 F. Supp. at 442-443. The Federal Circuit explained:

> Under these circumstances, the reduction to practice can be the most definitive corroboration of conception, for where the idea is in constant flux, it is not definite and permanent. A conception is not complete if the subsequent course of experimentation, especially experimental failures, reveals uncertainty that so undermines the specificity of the inventor's idea that it is not yet a definite and permanent reflection of the complete invention as it will be used in practice.

Burroughs Wellcome, 40 F.3d at 1229.

[46] Singh v. Brake, 222 F.3d 1362 (Fed. Cir. 2000).

[47] *Id.* at 1363-64.

[48] *Id.* at 1365.

loop deletion. Second, there was an issue as to whether the laboratory notebooks were useable as corroborative evidence, because they were dated years after the entries were made.

The Board held that Singh had not conceived of his invention prior to Brake's filing of his patent application; the Federal Circuit vacated the decision and remanded.[49] With respect to the first issue, the court extended the doctrine of no other substantial use, making it available for corroboration of conception as it had been available to corroborate reduction to practice.[50] With respect to the second issue, the court held that the Board erred in not considering the lab notebook entries, and that a totality of the corroborative evidence should have been considered—the lack of contemporary dating was only one factor.[51] In discussing the value of the undated lab notebooks, the court reopened the door for the separate analysis of conception and reduction to practice with respect to gene-related inventions. It noted that although the lab notebooks might not have satisfied the requirement for evidence to corroborate reduction to practice, they could corroborate conception, which had a lower requirement for corroboration.[52] The different standards implicitly dictate that with respect to DNA constructs, unlike gene sequences, conception does not necessarily require simultaneous reduction to practice.

From a practical perspective, this means three things. First, scientists should isolate and characterize a gene or sequence as early as possible. Second, patent applicants should not file applications claiming nucleotide sequences before they have the nucleotide sequences identified and characterized.[53] However, the standard for simultaneous conception and reduction to practice for DNA sequences is not necessarily extendable to other DNA-related inventions. Third, documentation is important; courts and one's adversaries will cite lab notebooks as evidence of invention or support to invalidate a patent.[54]

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[49] *Id.* at 1370.

[50] *Id.* at 1369. The doctrine of no substantial use holds that "when a putative inventor has obtained specific reagents with no 'substantial use' other than to make the claimed chemical compound, that evidence is of significant corroborative value." *Id.*

[51] *Id.* at 1370.

[52] *Id.* ("the standard of proof required to corroborate a reduction to practice, a more stringent standard that than required to corroborate a conception").

[53] Conception and enablement are distinct issues, but an enabling disclosure can be used to confirm conception. Burroughs Wellcome, 40 F.3d at 1231.

[54] *See, e.g.,* Purdue *et al.* v. Boehringer *et al.,* 98 F. Supp. 2d 362, 384-386 (S.D.N.Y. 2000) (analyzing testimony, declarations, and documents to determine conception and reduction to practice).

C. *Enablement*

A patent specification must "enable any person skilled in the art to which it pertains" to practice the invention.[55] The hypothetical person skilled in the art must be able to practice the invention without undue experimentation; however, the need to conduct some experimentation is not fatal.[56] With respect to DNA-related patents the courts have imposed a high bar.

> Tossing out the mere germ of an idea does not constitute an enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.[57]

But genetic sequences can be valid where they are of a scope appropriate to the invention disclosed by an applicant.[58] From a practical perspective, an applicant must show examples of more than a single organism in order to claim more.[59]

In *Enzo v. Calgene*,[60] Enzo appealed a decision that its claims pertaining to antisense technology were not enabled. Enzo's claims were directed to antisense technology generally, while the court thought that the specification contained little direction and only narrow working examples of applications outside of *E. coli*. In upholding the finding of invalidity based on a lack of enablement, the Federal Circuit noted:

> What is glaringly "missing" from the specifications is the disclosure of any direction or examples of how such an idea might be implemented in any cell other than *E. coli*. . . . [The] disclosure of practicing antisense in *E. coli* does not suffice to enable the practice of antisense in all categories of living matter.[61]

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[55] 35 U.S.C. § 112.

[56] Amgen, 927 F.2d at 1212. Factors to consider for whether there is undue experimentation include: "(1) the quantity of experimentation necessary, (2) the amount of direction or guidance, (3) the presence or absence of working examples, (4) nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." Enzo Biochem, Inc. v. Calgene, Inc., 188 F.3d 1362, 1371 (Fed. Cir. 1999) (quoting In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988)) (patents were invalid for trying to claim all of antisense technology). These factors are illustrative, not mandatory. Amgen, 927 F.2d at 1213.

[57] Enzo, 188 F.3d at 1374-1375 (quoting Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366 (Fed. Cir.), *cert. denied,* 522 U.S. 963 (1997)). But what is unpredictable now may later become predictable. *Id.* at 1375 n.10.

[58] Amgen, 927 F.2d at 1214.

[59] Enzo, 188 F.3d at 1375.

[60] *Id.* at 1362. One of the authors, David A. Kalow, was part of the trial team in the *Enzo* case.

[61] *Id.* at 1375.

Enzo and other case law reflect an unease of the courts with how to address the relationship between a genus and species with respect to biotechnology. For example, in the context of claims related to proteins, the single example of producing gamma-interferon in the dicotyledonous species of tobacco was held not to enable a biotechnician of ordinary skill to produce any type of mammalian protein in any type of plant cell.[62]

But the Federal Circuit has also held that it is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art.[63] Further, the Federal Circuit has noted that it "[does] *not* imply that patent applicants in art areas currently denominated as 'unpredictable' [will] never be allowed generic claims encompassing more than the particular species disclosed in their specification."[64]

This fine line between disclosing a species and claiming a genus suggests four things. First, applicants should disclose as many species as possible. Second, in a litigation, patent holders should emphasize the similarity between species. Third, alleged infringers should always argue that disclosure of one or a limited number of species does not enable the broad genus or other species. Fourth, defendants should look for problems confronted by the inventor or any skilled-in-the-art third party in practicing the invention in the same or other species.[65]

D. Written Description

In addition to enabling one skilled in the art to practice the invention, a patent specification must also provide a written description of the invention.[66] The specification must clearly indicate that the "inventor invented the claimed invention."[67] This requirement demands that the applicant describe the invention with all of its claimed limitations, and not only by describing what makes it obvious.[68]

There is an intuitive but unfortunately erroneous and asymmetrical relationship between the written description requirement of 35

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62 In re Goodman, 11 F.3d 1046, 1050 (Fed. Cir. 1993).

63 In re Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991).

64 Enzo, 188 F.3d at 1374 n.10 (quoting Vaeck, 947 F.2d 488, 496).

65 *Cf.* Johns Hopkins University *et al.* v. Cell Pro, Inc., 152 F.3d 1342 (Fed. Cir. 1998) (Alleged infringer failed to raise issue of material fact as to issue of enablement of genus. Evidence of failures was insufficient when there was no showing that individuals, who were undergraduate students in the inventor's lab, were skilled in the art.).

66 35 U.S.C. § 112 ("The specification shall contain a written description of the invention.").

67 Regents of The University of California v. Eli Lilly and Co., 119 F.3d 1559, 1566 (Fed. Cir. 1997), *cert. denied,* 523 U.S. 1081 (1998).

68 *Id.*

U.S.C. § 112, ¶ 1 and the non-obviousness requirement of 35 U.S.C. § 103. A description that does not render a claimed invention obvious does not sufficiently describe that invention for purposes of § 112, ¶ 1.[69] But a description that renders obvious a claimed invention does not necessarily satisfy the written description requirement.[70] Thus, for biotechnology patents, the written description requirement is but another statutory scenario under which the genus/species issue surfaces. "If conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, . . . then a description also requires that degree of specificity."[71]

The written description requirement serves to ensure that the inventor had possession, as of the filing date of the application relied upon, of the specific subject matter later claimed; how the specification accomplishes this is not material.[72] Thus, "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."[73] For example, 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 [an inventor] was in possession of the DNA."[74] However, akin to the standard for enablement, not every species would need to be described in order to describe the genus.[75] Thus, the Federal Circuit has held that in theory it does not require that the applicant describe exactly the subject matter that she claims, but the applicant must clearly allow a person of ordinary skill in the art to recognize that she invented what is claimed.[76] However, in practice an applicant who is seeking to patent a nucleotide sequence may find that she is only entitled to the specific sequences that are disclosed.[77]

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[69] *Id.* at 1567.

[70] *Id.*

[71] Fiers v. Revel, 984 F.3d 1164, 1171 (Fed. Cir. 1993); *see also* In re Alton, 76 F.3d 1168, 1171 (Fed. Cir. 1996).

[72] In re Alton, 76 F.3d. at 1172 (Fed. Cir. 1996).

[73] Eli Lilly, 119 F.3d at 1568; Fiers, 984 F.2d at 1171.

[74] Fiers, 984 F.2d at 1171; *see also,* Eli Lilly, 119 F.3d at 1567 ("The name cDNA is not itself a written description; it conveys no distinguishing information concerning its identity.").

[75] *Id.* at 1568.

[76] Union Oil Co. of California v. Atlantic Richfield Co. *et al.*, 208 F.3d 989, 997 (Fed. Cir. 2000).

[77] One should note that in the context of chemical cases, the Federal Circuit has been clear and imposed a less rigorous standard than in biotechnology cases: "The written description requirement does not require identical descriptions of claimed compounds, but it requires enough disclosure in the patent to show one of ordinary skill in this art that the inventor '*invented what is claimed.*'" *Id.*, 208 F.3d at 1001 (quoting Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563 (Fed. Cir. 1991)).

In *The Regents of the University of California v. Eli Lilly*,[78] the two patents in suit related to recombinant DNA technology. The patents disclosed rat insulin-encoding DNA but claimed broader genuses and other species' insulin-encoding cDNA, e.g., mammals, vertebrates, and humans.[79] The court held the applicant was not entitled to those claims.

The descriptions of rat insulin cDNA, a general method of producing human insulin cDNA, and human insulin A and B chain amino acid sequences were not enough to claim the human cDNA.[80] This information, if it were in the prior art, would not render the sequence obvious; therefore, these references could not provide an adequate written description.[81] Similarly, the rat cDNA was not enough to provide a written description of the genuses of mammalian or vertebrate cDNA. A precise definition was required for chemical species.[82] The Federal Circuit explained:

> In claims to genetic material . . . a generic statement such as "vertebrate insulin DNA" or "mammalian insulin DNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is . . . .
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> . . . A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus under § 112, ¶ 1, by showing the enablement of a representative number of species within the genus.[83]

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[78] 119 F.3d 1559.

[79] *Id.* at 1567.

[80] *Id.*

[81] *Id.*

[82] *Id.* at 1568.

[83] *Id.* (footnote omitted). *See also* Fiddes v. Baird, 30 U.S.P.Q.2d 1481, 1483 (Bd. Pat. App. & Int. 1994) (Patent teaching no amino acid or DNA sequences for any mammalian FGF other than bovine pituitary FGF does not provide written description for the broad class of FGFs.).

The strategies for satisfying the written description requirement are similar to those required for enablement. Applicants and patent owners should describe as much as possible and argue the similarities across species. Their adversaries should emphasize the differences between species and the absence of any species covered by a genus claim.

The Patent & Trademark Office has not been unsympathetic to the concerns over the Federal Circuit's firm stance on written description requirements. On December 21, 1999, the Patent & Trademark Office issued its Revised Interim Guidelines for Examination of Patent Applications under 35 U.S.C. §112, ¶1, "Written Description" Requirement: Request for Comments, in which it attempted to address practitioners' concerns about the recent developments of the written description requirement in both the Patent & Trademark Office and the courts.[84] On January 5, 2001, the Patent & Trademark Office issued its *Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1, "Written Description Requirement,"* which superseded the interim guidelines.[85] Unfortunately, the guidelines provide little help, repeatedly stating the Patent Office is bound by Federal Circuit law. With respect to the troublesome issue of providing a satisfactory written description to claim a genus, it noted merely that when one wants to claim a genus, one needs to disclose a sufficient variety of species, the number will vary inversely with the skill and knowledge in the art, and for an unpredictable art disclosure of a single species is not enough to claim the genus.[86]

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The four areas of invalidity described above, as applied to genetic/biotechnology patents, will likely provide the foundation for analyzing future genetic/biotechnology patents, including bioinformatics patents.

II.
THE INCARNATION OF BUSINESS METHODS PATENTS

Two decades ago, the Supreme Court noted that "laws of nature, physical phenomenon and abstract ideas" were not patentable.[87] Based on this statement, one might think that naturally occurring nu-

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[84] 64 Fed. Reg. 71427.

[85] 66 Fed. Reg. 1099.

[86] *Id.* at 1106.

[87] Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (The product of "a new bacterium with markedly different characteristics from any found in nature and . . . having the potential for significant utility . . . is patentable under [35 U.S.C.] § 101.").

cleotide sequences are not patentable. But "[a]lthough patent claims to naturally occurring DNA might be expected to trigger the 'products of nature' rule, courts have upheld patent claims covering 'purified and isolated' DNA sequences as new compositions of matter resulting from invention."[88] Thus, "[a]lthough there remain the traditional categories that have never been viewed as patentable subject matter, *viz.*, laws of nature, natural phenomena, and abstract ideas, the policy underlying the patent system fosters its application to all areas of technology-based commerce."[89]

In the summer of 1998, in *State Street,* the Federal Circuit visited the issue of patentability and made clear that business methods were not *per se* unpatentable.[90] The Court also held that any bar to patenting mathematical algorithms was valid "only to the extent that [the claimed invention] represents an abstract idea."[91] Once a mathematical algorithm is applied in a useful way, it is patentable.[92] Thus, one of the themes of *State Street* was that the 35 U.S.C. § 101 utility requirement should not bar the patentability of abstract ideas that, as applied, generate useful, concrete, or tangible results.

In light of *State Street*, "many companies are running to the PTO with Internet-related or e-commerce programs."[93] Although these applications involve the Internet or other computer software, they are often patents for business methods. "Business methods include the way a business is structured, managed, organized and/or carried out."[94] Thus, this may include distribution and sales procedures, suppliers and customer service methods, and business-customized software and information systems.

State Street, on its face, has nothing to do with biotechnology patents. The patent at issue involved a method for financial institutions to pool money and to invest it as a partnership.[95] However, *State Street* is not limited to financial or e-commerce businesses. Its holding is now being and will continue to be felt throughout the patent world. In the context of genetic/biotechnology patents, this will lead to a significant

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88 J. Miller, *Patent Law and Human Genomics*, 26 CAP. U.L. REV. 893, 907 (1997).

89 Pioneer Hi-Bred International, Inc. v. J.E.M. AG Supply, Inc. *et al.*, 200 F.3d 1374, 1376 (Fed. Cir. 2000).

90 149 F.3d at 1375 ("We take this opportunity to lay this ill-conceived [business method] exception to rest.").

91 *Id.* at 1373 n.4.

92 *Id.*

93 Steven Friedman *et al., State Street Bank and Trust Company v. Signature Financial Group, Inc.: Seeking The Keys To Cyberspace,* 589 PLI/Pat 31, 54 (2000).

94 Michael E. Melton, *The Business of Business Method Patents,* 589 PLI/Pat 97, 102 (2000).

95 *State Street*, 149 F.3d at 1368.

increase in biology-related business method patent applications, most specifically as computer-related bioinformatics patent applications. As one commentator has noted, "academic institutions and companies have already recognized the benefits of creating faster and more accurate gene and protein programs, algorithms and databases."[96] The pursuit of patents relating to these benefits is inevitable.

In addition to prompting a flood of bioinformatics patents, the most important of which someday will be litigated, *State Street* will also prove a source of support for litigants who are faced with charges of invalidity under 35 U.S.C. § 101. As described above, *State Street* implies a policy of viewing the scope of what is patentable as very broad and not barring activity and products of technology as applied to the business world. The Patent Office, however, might not be extending the sentiment of the broad holding of *State Street* to genetic/biotechnology patent applications.

On December 21, 1999, the Patent and Trademark Office issued the *Revised Utility Examination Guideline: Request for Comments.*[97] The requests for comments were prompted by the public comment on the interim Written Description Guidelines regarding the patentability of ESTs.[98] Under the interim standard, Examiners were to reject claims under 35 U.S.C. § 101 if the claimed invention did not have a well-established utility and there was no credible assertion of specific and substantial utility by the applicant.[99]

On March 1, 2000, the Patent Office announced that it was offering training materials for Interim Written Description and Utility Guidelines.[100] The examples of the Revised Interim Utility Guidelines Training Materials provide thirteen samples of when applicants may expect and not expect rejections under 35 U.S.C. § 101.[101] "With respect to DNA Fragments or ESTs, the USPTO will be looking for a utility particular to the DNA fragment or EST that exists in a real-

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96 Datagheib-Vinarov, 4 MARQ. INTELL. PROP. L. REV. at 159.

97 64 Fed. Reg. 71440.

98 *Id.* at 71441. The Patent Office received "[m]any comments (that) stated that sufficient patentable utility has not been shown when the sole disclosed use of an EST is to identify other nucleic acids whose utility was not known, and the function of the corresponding gene is not known."

99 *Id.*

100 *PTO Offers Training Materials for Interim Written Description and Utility Guidelines,* P.T.O. Press Release #00-15, March 1, 2000. The revised utility guidelines can be found at http://www.uspto.gov/web/offfices/pac/utility/utilityguide.pdf. The period for comment on the guidelines closed March 22, 2000. *Id.*

101 Revised Interim Utility Guidelines Training Materials are available at http://www.uspto.gov/web/offices/pac/utility/utiltiyguide.pdf.

world context."[102] With respect to single nucleotide polymorphisms, the focus may be on whether there is a causal relationship between the variation and the disease.[103]

On January 5, 2001, the Patent Office issued a revised version of utility guidelines that superseded the Revised Interim Utility Guidelines but emphasized that, for the most part, the Patent Office would be sticking to the rubric announced in the interim standard, which focuses on specific, substantial, and credible utility in terms of determining whether an applicant has complied with 35 U.S.C. § 101.[104] The regulations summarized: "An invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (*e.g.,* properties of application of a product or process), and (2) the utility is specific, substantial, and credible."[105] A specific and substantial utility excludes utilities that are "throw-away," "insubstantial," or "nonspecific";[106] thus, there is some hurdle being imposed by the Patent Office. The extent to which this affects the issuance and validity of patents will surely be developed in future administrative proceedings and case law.[107]

Thus, the tension between the new utility guidelines and the tone of *State Street* is clear. With this uncertainty come options for the litigants. And with only a few business method cases decided in light of

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[102] Thomas J. Kowalski, *Analyzing the USPTO's revised utility guidelines,* 18 NATURE BIOTECHNOLOGY 349, March (2000).

[103] *Id.* at 350. "With respect to DNA fragments or ESTs, the USPTO will be looking for a utility particular to the DNA fragment or EST that exists in a real-world context." *Id.* at 349.

[104] 66 Fed. Reg. 1092.

In these recent guidelines, a number of comments by the public and responses thereto by the Patent Office were published. These comments are harbingers of the arguments that will likely be presented in courts during future biotechnology patent litigations. A significant number of them were policy based, and as the Patent Office noted, more appropriately directed to Congress. For example, commentators objected to the patenting of genes because they are products of nature.

One noteworthy difference, especially for patent prosecutors, between the interim guidelines and the guidelines that replaced them was that under the newer standard if the Examiner does not perceive a well-established utility, a rejection should be entered, and the Examiner need not prove that one does not exist. *Id.* at 1098.

[105] *Id.* at 1095.

Interestingly, the Patent Office has directed its Examiners to make rejections for a lack of utility, not only under 35 U.S.C. § 101, but also under 35 U.S.C. § 112. *Id.* at 1098.

[106] *Id.* at 1098

[107] Although these regulations do not have the effect of law, they will likely be used as persuasive authority by creative litigators.

State Street, there is little precedent by which to develop an instinct as to how those patents will be treated.[108]

III.
PREDICTIONS FOR THE FUTURE AND PRACTICE TIPS

Regardless of the side on which genetic/biotechnology patent litigants find themselves, they must be prepared for new case law to develop as courts synthesize *State Street,* more traditional biotechnology patent doctrine, and the utility requirements as applied to genetic/biotechnology patents. Bioinformatics patents are a mesh of biology and computer patents. Applicants and litigants need to determine whether to emphasize the biology or computer aspects of their inventions.[109] Their strategies will depend in part on the answers to questions such as: Will the Patent Office, and the courts, continue to be lenient in terms of 35 U.S.C. § 103 and demanding in terms of 35 U.S.C.§ 112, as they have in the context of biotechnology applications? Will the standards be different for the business methods type patents, which are only now beginning to be litigated, and the bioinformatics patents, which have not been litigated? Will *State Street* reemphasize that, despite 35 U.S.C. § 101, anything under the sun is patentable if made by man,[110] or will there be an increased number of rejections based on a lack of utility in light of the *Utility Examination Guidelines* issued January 5, 2001?

These questions and others will all be answered as the effects of the completion of the Human Genome Project are appreciated by society, new patent applications (especially bioinformatics patent applications) are filed and litigated, and the courts apply Patent Law. As with most developments in the law, the journey will likely be long and painful, but in genetic/biotechnology patents, entrepreneurs cannot afford to be inattentive.

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[108] As of March 11, 2001, only five reported court decisions (one in the dissenting opinion) have cited *State Street. See* Festo v. Skoetsu Kinzoku Kogyo Kabuskiki Co., 234 F.3d 228 (Fed. Cir. 2000); WMS Gaming, Inc. v. International Game Technology, 184 F.3d 1339 (Fed. Cir. 1999); AT&T Corp. v. Excel Communications, Inc., 172 F.3d 1352 (Fed. Cir. 1999); Hughes Aircraft Co. v. United States, 148 F.3d 1384 (Fed. Cir. 1998); AT&T v. Excel Communications, Inc., 52 U.S.P.Q.2d 1865 (D. Del. 1999). Additionally, *State Street* has been cited once by the Board of Patent Appeals and Interferences. *See* Ex parte Donner, 53 U.S.P.Q.2d 1699 (Bd. Pat. App. & Interf. 1999).

[109] For a suggestion of the types of claims that might be appropriate for bioinformatics patent applications, see Mark DeLuca, State Street and Its Effect on the Biotechnology and Bioinformatics Industries, SIXTEENTH ANNUAL JOINT PATENT SEMINAR, I-29 (April 11, 2000).

[110] 149 F.3d at 1373.