

Making Sense out of Antisense: The Enablement Requirement in Biotechnology After *Enzo Biochem v. Calgene*

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INTRODUCTION

The progression of genetic science¹ in the last three decades has brought with it medical and technical advances² unimaginable to the world prior to the discovery³ of the structure of DNA forty-seven years ago. With the recent advance of countless new biological discoveries has come the need to examine complex questions of morality, religion, politics, and economics.⁴ Included in this need for examination, and affected by genetic technology perhaps more than any other realm, are the complex questions raised in the law by these modern technological miracles.⁵ Genetic technology has affected nearly every area of the law,⁶ and one of the areas most strongly influenced has been patent law.

A good example of biotechnology's influence on patent law is the controversial attempt at patenting partial sequences of copy DNA ("cDNA") called "expressed sequence tags" ("ESTs").⁷ In 1991, the National Institutes of Health filed patent

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1. See generally GEORGE M. MALACINSKI & DAVID FREIFELDER, *ESSENTIALS OF MOLECULAR BIOLOGY* (3d ed. 1998). Biotechnology or genetic technology includes modern molecular biology techniques that have been developed since the discovery of the structure of DNA in 1953. Molecular biology focuses upon the form and function of genetic material and molecular units that act on such material. *Id.* at 3-5; JAMES D. WATSON ET AL., *MOLECULAR BIOLOGY OF THE GENE* 74 (4th ed. 1987).

2. See *id.* at 409-37; see also JEREMY RIFKIN, *THE BIOTECH CENTURY: HARNESSING THE GENE AND REMAKING THE WORLD* 15-32 (1998).

3. See Alfred E. Mirsky, *The Discovery of DNA*, *SCI. AM.*, June 1968, at 78-88.

4. See, e.g., Ronald Kotulak, *Taking License with Your Genes*, *CHI. TRIB.*, Sept. 12, 1999, at A1; MALACINSKI & FREIFELDER, *supra* note 1, at 409-37.

5. See, e.g., *United States v. Dionisio*, 410 U.S. 1, 8 (1973) (discussing the Court's conclusion in *Schmerber v. California*, 384 U.S. 757 (1966), that blood samples used for genetic forensic tests are a seizure for Fourth Amendment purposes); *Johnson v. Calvert*, 851 P.2d 776 (Cal. 1993) (holding the genetic mother and not the gestational surrogate mother to be the true mother); *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990) (discussing property rights of cellular research material extracted from a patient at a hospital); *Cornelio v. Stamford Hosp.*, 717 A.2d 140 (Conn. 1998) (holding that an individual loses her property right to genetic and cell material when she allows a doctor to remove it); *In re Chattman*, 393 N.Y.S.2d 768 (N.Y. App. Div. 1977) (granting right to an adopted woman to see her biological parent's genetic history for her own health problems).

6. See *supra* note 4.

7. ESTs are portions of DNA that have a known sequence but no known function. Until a function is discovered, the only practical use for the ESTs are as probes to sequence other

applications for a large number of ESTs and created a storm of controversy throughout the scientific and legal communities.⁸ The fundamental issue at the heart of the controversy, at its simplest level, was whether a DNA sequence with an unknown function could be patented.⁹ Many opponents of the ESTs patent application argued that until researchers discovered what gene the DNA encoded, a patent of the naked DNA sequence would be premature. The ensuing litigation and large amounts of legal commentary¹⁰ concerning the ESTs patent issue has done much to shape patent-law doctrine.

Although ESTs technology has been at the forefront of the patent debate for the last decade, another technology has emerged that shares many of the same problems of patentability. The technology known as antisense genetic technology is a method of blocking the expression of specifically chosen genes in an organism.¹¹ Such a system has great potential for valuable applications in medical treatment and in countless other fields.¹² The first major antisense technology litigation concerned its agricultural applications.¹³ Calgene, Inc., an agricultural biotechnology company, marketed a tomato in which antisense-technology was used to block the gene responsible for quick ripening, and thus increase the tomato's shelf life. Calgene's tomato was challenged by Enzo Biochem, Inc., who owned a general patent on antisense technology.¹⁴ Enzo failed in its challenge, and not only was Calgene's tomato found not to infringe Enzo's patents, but also Enzo's patents were also found to be invalid for lack of enablement.¹⁵

This Note will focus on how recent developments in patent-law doctrine affected this litigation, and what this litigation suggests for the future of patent law in biotechnology. In particular, this Note examines the enablement requirement of section 112 of the Patent Act,¹⁶ and the unique problems the enablement requirement

DNA segments. For a technical discussion of ESTs, see Andrew T. Kight, *Pregnant with Ambiguity: Credibility and the PTO Utility Guidelines in Light of Brenner*, 73 IND. L.J. 997 (1998); Richard A. Epstein, *Property Rights in cDNA Sequences: A New Resident for the Public Domain*, 3 U. CHI. L. SCH. ROUNDTABLE 575 (1996).

8. See Kight, *supra* note 7, at 998-99. Incidentally, the person at the NIH who attempted to get the ESTs patented was J. Craig Venter. Venter was recently in the news for being the CEO of Celera Genomics, the leader in the privately funded branch of the Human Genome Project. See Sharon Begley, *Decoding the Human Body*, NEWSWEEK, Apr. 10, 2000, at 54.

9. Kight, *supra* note 7, at 998-99.

10. See generally Rebecca S. Eisenberg & Robert P. Merges, *Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial cDNA Sequences*, 23 AM. INTELL. PROP. L. ASS'N Q.J. 1 (1995); Melissa L. Sturges, *Who Should Hold Property Rights to the Human Genome? An Application of the Common Heritage of Humankind*, 13 AM. U. INT'L L. REV. 219 (1997).

11. See MALACINSKI & FREIFELDER, *supra* note 1, at 182-83, 429.

12. *Id.*

13. See *Enzo Biochem, Inc. v. Calgene, Inc.*, 14 F. Supp. 2d 536 (D. Del. 1998), *aff'd in part and vacated in part* by 188 F.3d 1362 (Fed. Cir. 1999).

14. *Id.* at 541.

15. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362 (Fed. Cir. 1999). The enablement requirement requires a patent applicant to adequately disclose the invention so that others may practice it. See *infra* text accompanying notes 38-44.

16. 35 U.S.C. § 112 (1994).

poses to unpredictable arts such as biotechnology. The decision in *Enzo Biochem, Inc. v. Calgene, Inc.*¹⁷ signals the Federal Circuit's continued trend of making broad patent applications difficult to obtain in the biotechnological arts. This Note argues that the Federal Circuit should not expand the enablement requirement any further and, in some instances, should loosen the requirements, or else a drastic chilling effect in biotechnology research investment will occur.

Part I of this Note will give a basic overview of section 112 and the enablement requirement. Part II will discuss the scientific foundations behind antisense technology. Part III will examine the specific application of the enablement requirement to antisense technology in *Enzo* and discuss the difficulty of applying the enablement requirement to the biotechnological arts.

I. OVERVIEW OF SECTION 112 AND ITS ENABLEMENT REQUIREMENT

The power of the U.S. government to grant patents lies in Article I, Section 8, Clause 8 of the Constitution.¹⁸ Demonstrating the importance of patent protection to the Founding Fathers,¹⁹ the first Congress passed the Patent Act of 1790 as one of its first official acts.²⁰ Since that time, the Patent Act has continued to be revised and promulgated to its current form.²¹ In general, a patent applicant will be successful in his application only if the patent is novel,²² useful,²³ and nonobvious.²⁴ Although

17. 188 F.3d 1362 (Fed. Cir. 1999).

18. "The Congress Shall have Power . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries." U.S. CONST. art. I, § 8, cl. 8; see also Brian P. O'Shaughnessy, *The False Inventive Genus: Developing a New Approach for Analyzing the Sufficiency of Patent Disclosure within the Unpredictable Arts*, 7 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 147, 155-56 (1996) (calling the provision "a rare instance in which the Founding Fathers coupled an enumerated power with a specific objective").

19. Thomas Jefferson was the driving force behind the U.S. patent system and could be considered the father of patent law in this country. He wrote "nobody wishes more than I do that ingenuity should receive a liberal encouragement." Letter from Thomas Jefferson to Oliver Evans (May 2, 1807), in 5 THE WRITINGS OF THOMAS JEFFERSON 74, 76 (H.A. Washington ed., New York, Riker, Thorne & Co. 1854). For a discussion of Jefferson's patent philosophy and his many contributions to the field, see *Graham v. John Deere Co.*, 383 U.S. 1 (1966).

20. Patent Act of 1790, ch. 7, 1 Stat. 109-12 (April 10, 1790); see also ROBERT P. MERGES, ET AL., *INTELLECTUAL PROPERTY IN THE NEW TECHNOLOGICAL AGE* 126 (1997).

21. Major revisions to the Patent Act occurred in 1836, 1952, and 1982. See MERGES ET AL., *supra* note 20, at 126-28.

22. 35 U.S.C. § 102 (1994). Novelty requires the claimed invention not to have been previously practiced in the public domain. See MERGES ET AL., *supra* note 20, at 168.

23. 35 U.S.C. § 101. Utility requires that the claimed invention have some type of useful purpose. See MERGES ET AL., *supra* note 20, at 163-65.

24. 35 U.S.C. § 103. Nonobviousness requires that the claimed invention add something to the prior art and not simply be a logical expansion of a previous invention. See MERGES ET AL., *supra* note 20, at 207.

these are the three main requirements of patentability,²⁵ other requirements also exist.²⁶ Of these additional requirements, the disclosure requirement of section 112²⁷ of the Patent Act has traditionally been important in determining whether to grant a patent. Recent developments in biotechnology patent law have made the section 112 requirements increasingly important.²⁸

A. Section 112

The basic policy behind the section 112 disclosure requirement is to ensure that the public receives an actual benefit from the applicant's patent.²⁹ Granting a patent to an inventor gives the inventor a limited monopoly in her invention by which she is allowed to manufacture, use, and sell the invention to the exclusion of all other competitors for a limited time. In exchange for this economic advantage, the inventor must adequately disclose his invention to the public in a manner that allows the public to fully understand the invention.³⁰ In this way, both the public and the inventor benefit: the inventor gains a competitive economic advantage, and the public shares in the latest discoveries in the art.

If an inventor was granted a patent without disclosing to the public exactly what the invention was or how it worked, the inventor would benefit, and the public would not only remain ignorant of the new discovery, but also would not know if their own work was infringing on the patent.³¹ The policy of section 112 is to prevent such problems. These types of problems arise quite frequently in the biotechnological arts.³²

Section 112 is divided into six paragraphs which detail the requirements for what is needed in the specifications and claims of a patent application.³³ This Note will

25. *E.g.*, *United States v. Adams*, 383 U.S. 39, 48 (1966).

26. The patent application must also be appropriate subject matter for patent, 35 U.S.C. § 101, and must meet the disclosure requirements of 35 U.S.C. § 112. *See MERGES ET AL.*, *supra* note 20, at 129.

27. Some commentators consider the disclosure requirement to be part of the utility requirement. *See, e.g.*, *Eisenberg & Merges*, *supra* note 10, at 4; DONALD S. CHISUM, *CHISUM ON PATENTS: A TREATISE ON THE LAW OF PATENTABILITY, VALIDITY AND INFRINGEMENT* § 7.03[6] (1978). Regardless of where the disclosure requirement falls for organizational purposes, section 112 is the appropriate focus for proper analysis of disclosure.

28. *See infra* Part III.C.1.

29. *See O'Shaughnessy*, *supra* note 18, at 149 (describing a patent grant as a social contract).

30. *See Emanuel Vacchiano*, *It's a Wonderful Genome: The Written-Description Requirement Protects the Human Genome from Overly-Broad Patents*, 32 J. MARSHALL L. REV. 805, 813 (1999) ("Congress enacted a series of laws that establish a quid pro quo between an inventor and the rest of society.").

31. *See Mark A. Lemley*, *Intellectual Property and Shrinkwrap Licenses*, 68 S. CAL. L. REV. 1239, 1276 n.168 (1995) ("The effect of [section 112] is twofold: by requiring public disclosure, the patent laws put the invention unambiguously into the public domain . . . [and] help[] ensure that the claim is for no more than the patentee has invented.").

32. *See infra* Part I.E.

33. The specification describes an invention generally. ROBERT L. HARMON, *PATENTS AND THE FEDERAL CIRCUIT* 168 (4th ed. 1998). The claims (that are technically part of the

focus on the first paragraph of section 112.³⁴ The first paragraph of section 112 is generally considered to have three distinct requirements: written description, enablement, and best mode.³⁵ The best-mode³⁶ and written-description³⁷ requirements

specification) provide what is commonly referred to as the “metes and bounds” of the patent and set up boundaries of the property right conferred by the patent. *See generally id.* at 187-88 (“It is the claim, not the specification, that distinguishes what infringes from what does not.”).

34. The sixth paragraph of section 112 pertains to “means-plus-function” claims and has been the subject of recent debate. *See generally* Fidel D. Nwamu, *Does Your Claim Conform to Means-Plus-Function Format under Section 112, Paragraph Six?: O.I. Corp. v. Tekmar, Co.*, 6 J. INTEL. PROP. L. 189 (1999). However, paragraph six is beyond the scope of this Note. The second paragraph of section 112 pertains to the claims of a patent and is generally considered to have two requirements. The claims must “point out what the invention is in such a way as to distinguish it from the prior art . . . and to define the scope of protection afforded by the patent.” HARMON, *supra* note 33, at 187. Although *Enzo* did raise some possible paragraph two issues, analysis of paragraph two is beyond the scope of this Note.

35. *See* Thomas L. Irving et al., *The Significant Federal Circuit Cases Interpreting Section 112*, 41 AM. U. L. REV. 621 (1992); O’Shaughnessy, *supra* note 18, at 159. The text of section 112, paragraph one reads:

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.

35 U.S.C. § 112 (1994).

36. The best-mode requirement requires an inventor to disclose the best method of carrying out the invention. MERGESET AL., *supra* note 20, at 228. This requirement prevents an inventor from holding back crucial information needed to best practice the patent, while at the same time having all of the protections of a successful patent granted to him. The best-mode requirement ensures that the “bargain” between the inventor and the public remains fair and that the public is not cheated out of what they deserve by way of disclosure in exchange for the patent monopoly. Leora Ben-Ami et al., *Biotech Patent Law Developments, in FIFTH ANNUAL INSTITUTE FOR INTELLECTUAL PROPERTY LAW 1999*, at 555, 578 (PLI Intellectual Prop. Course Handbook Series No. 573, 1999); GLENN W. RHODES, PATENT LAW HANDBOOK § 1.06[3] (1997-98 ed.).

37. The function of the written description requirement is to ensure that the patent applicant was actually in possession of the item being claimed at the time the applicant filed. *See* RHODES, *supra* note 36, § 1.06[1]. In *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the Federal Circuit held that a DNA fragment encoding a specific protein was not enabled because the patent only disclosed a method of obtaining the fragment, not the actual sequence. *Id.* at 1168. Therefore, the patent applicant had not shown that the actual gene segment was in his possession. *See* Vacchiano, *supra* note 30, at 816-17. In a case with similar facts as *Enzo*, the Federal Circuit said a patent disclosing a rat DNA sequence for a gene and claiming the human sequence failed the written description requirement, because the human DNA sequence was not in the applicant’s possession at the time of filing. *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566-69 (Fed. Cir. 1997). Enablement is closely related to written description, but in enablement analysis, the possession of the claimed invention is immaterial as long as the claimed material is “easy” to get from the patent disclosure. *But see* Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 BERKELEY TECH. L.J. 615, 633 (1998) (arguing that *Lilly* has turned the written description requirement into a “super-enablement” requirement).

are not relevant to this Note's discussion of antisense technology.

B. Enablement

The purpose of the enablement requirement is to ensure that the patent applicant is not claiming more than the patent applicant actually has discovered.³⁸ In order to be enabled, a patent specification must teach one "skilled in the art" to make and use the invention without undue experimentation.³⁹ The real touchstone of enablement is whether the patent teaches one of ordinary skill how to practice the invention. The invention cannot just throw out "a germ of an idea" or a starting point for research.⁴⁰ However, the amount of "teaching" needed in a patent depends upon the invention's complexity, breadth, and predictability.

One of the earliest and most famous examples of a patent failing on enablement grounds is Samuel Morse's attempt to patent the use of any form of electromagnetism to communicate at a distance.⁴¹ The Supreme Court held this claim invalid because of its generality: "He claims an exclusive right to use a manner and process which he has not described and indeed has not invented . . . [T]he claim is too broad."⁴²

Another classic case regarding lack of enablement concerned an electric company's attempt to patent "[a]n incandescing conductor for an electric lamp, of carbonized fibrous or textile material."⁴³ Citing Thomas Edison's long and laborious experiments to determine adequate materials for light bulbs, the Supreme Court reasoned that this patent claim was too broad in its claim of any material capable of being used as a light bulb filament and held the patent claim was not enabled.⁴⁴

The enablement requirement is important in two stages of patent protection. First, the patent applicant must overcome the enablement hurdle during the prosecution stage of the patent.⁴⁵ Second, the patent can be challenged for lack of enablement during patent litigation.⁴⁶ Many commentators have dismissed the enablement requirement in the litigation arena as unrealistic.⁴⁷ However, in the biotechnological

38. See MERGES ET AL., *supra* note 20, at 216.

39. See Rochelle K. Seide & Janet M. MacLeod, *Drafting Claims for Biotechnology Inventions*, in SEVENTH ANNUAL PATENT PROSECUTION WORKSHOP: ADVANCED CLAIM DRAFTING AND AMENDMENT WRITING 1997, at 353, 431 (PLI Pat., Copyrights, Trademarks, and Literary Prop. Course Handbook Series No. 501, 1997).

40. Genentech, Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1365-68 (Fed. Cir. 1997).

41. See WILLIAM H. FRANCIS & ROBERT C. COLLINS, CASES AND MATERIALS ON PATENT LAW 431 (4th ed. 1995); MERGES ET AL., *supra* note 20, at 216.

42. O'Reilly v. Morse, 56 U.S. (15 How.) 62, 113 (1853).

43. The Incandescent Lamp Patent, 159 U.S. 465, 468 (1895).

44. *Id.* at 473-76.

45. Prosecution of a patent pertains to the process of obtaining the patent from the U.S. Patent and Trademark Office.

46. Litigation of a patent pertains to the process in which one adverse party challenges the validity or the possible infringement of another party's patent.

47. See, e.g., Jeffrey R. Kuester, *Effective §102, 103, 112 Defenses: What Can Defendants Do to Win with Them Today?*, in PATENT LITIGATION 1998, at 933, 957 (PLI Pat., Copyrights, Trademarks, and Literary Prop. Course Handbook Series No. 531, 1998) ("It is normally very difficult to invalidate a patent for lack of enablement . . .").

arts, the enablement requirement has become a legitimate factor for invalidity challenges in patent litigation.

C. Enablement in Unpredictable Arts: The Wands Factors

The reason for the enablement requirement's special pertinence to the biotechnological arts has to do with the intrinsic nature of biotechnology. Biotechnology is an unpredictable art.⁴⁸ The very nature of biotechnology involves the manipulation of and experimentation with complex genetic systems in living cells.⁴⁹ Avoiding trial and error experiments and unpredictable results in this field is impossible.⁵⁰ Unpredictability in a field has a huge impact on enablement analysis, because as the predictability of a field increases, the enablement requirement becomes easier to satisfy.⁵¹ If a field is predictable, the art disclosed in the specification becomes easier to practice without undue experimentation and unexpected results. However, if the field is unpredictable, the patent's teachings will be harder to practice successfully, with failure to practice and the need for experimentation becoming more likely.⁵² High unpredictability in a field makes it increasingly difficult for one of ordinary skill in the art to practice the full scope of the invention without undue experimentation.⁵³ Therefore, the more unpredictable the field, the more difficult it is to satisfy the enablement requirement.

In *Ex parte Forman*, the Patent Board of Appeals developed a framework with which to analyze the enablement requirement in the unpredictable arts.⁵⁴ The Federal Circuit adopted these factors for their own enablement analysis in *In re Wands*.⁵⁵ The factors are generally referred to as the "Wands factors" and include:

- (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the

48. See *In re Goodman*, 11 F.3d 1046, 1050-51 (Fed. Cir. 1993) (discussing the field's unpredictability); O'Shaughnessy, *supra* note 18, at 165-66 ("[L]iving materials such as microorganisms or cultured cells, and other aspects of biochemistry and genetic manipulation . . . are generally categorized as among the unpredictable arts."); Seide & MacLeod, *supra* note 39, at 435 ("Genetic engineering and immunological inventions are considered highly unpredictable technologies.").

49. See *supra* note 1.

50. See Kate H. Murashige, *Section 102/103 Issues in Biotechnology Patent Prosecution*, 16 AIPLA Q.J. 294, 297-300 (1988-89).

51. See Seide & MacLeod, *supra* note 39, at 435 ("In allegedly unpredictable fields . . . the scope of enablement varies inversely with the scope of protection.").

52. See Karen S. Cannady, *The Wright Enabling Disclosure for Biotechnology Patents*, 69 WASH. L. REV. 455, 461-62 (1994); Ellen P. Winner, *Enablement in Rapidly Developing Arts—Biotechnology*, 70 J. PAT. TRADEMARK OFF. SOC'Y 608, 608-09 (1998).

53. See *In re Vaecck*, 947 F.2d 488, 494-96 (Fed. Cir. 1991) ("Where . . . a claimed genus represents a diverse and relatively poorly understood group of microorganisms, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a 'predictable' factor such as a mechanical or electrical element.").

54. *Ex parte Forman*, 230 U.S.P.Q. (BNA) 546, 547 (Bd. of Patent Appeals & Interferences 1986).

55. 858 F.2d 731, 737-38 (Fed. Cir. 1988).

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.⁵⁶

The *Wands* factors are generally analyzed only in the unpredictable arts⁵⁷ and, if used at all, are not mandatory but illustrative.⁵⁸

The *Wands* factors analysis requires an inherent internal balancing. For example, the quantity of experimentation needed to practice an invention should not be analyzed in a vacuum; rather, the nature of the experiments and the level of difficulty should be included in the analysis.⁵⁹ Thus in *Wands*, although a large amount of experimentation was needed to practice the invention,⁶⁰ the experimentation was not difficult and was routine in the field, so the patent was held to be enabled. Similarly, if the claims of a patent are broad enough to encompass a wide range of areas not described in the specification, then the patent must contain more detailed examples and guidance.⁶¹ Therefore, a certain amount of flexibility exists within the *Wands* factors.

D. Enablement and Biotechnology

The Federal Circuit analyzes the nature of the art when determining enablement.⁶² Therefore, biotechnology patents must be examined through a field-specific lens. In *Amgen, Inc. v. Chugai Pharmaceutical Co.*,⁶³ the applicant claimed all possible DNA sequences that would encode for a protein and all of the protein's analogs, while only describing how to make a few analogs.⁶⁴ The purpose of such a claim was to prevent a subsequent party from subtly changing the amino acid or the DNA sequence in an attempt to invent around the disclosed invention. The Federal Circuit stated, however, that the patent was too broad and not enabled because, although "it is not necessary that a patent applicant test all the embodiments of his invention," an applicant must disclose "how to make and use enough sequences to justify grant of the claims sought."⁶⁵ The Federal Circuit held that the patent did not enable one skilled in the art the ability to practice the full scope of the invention.⁶⁶

56. *Id.* at 737.

57. *See Cannady, supra* note 52, at 459.

58. *See Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999) (citing *Amgen v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)).

59. *See Cannady, supra* note 52, at 460.

60. Somebody skilled in the art would have had to screen 134 hybridomas. *Id.*

61. *Id.* at 460-61.

62. Some commentators have noted that "[e]nablement is a peculiarly fact-driven inquiry." Eisenberg & Merges, *supra* note 10, at 44.

63. 927 F.2d 1200 (Fed. Cir. 1991).

64. Due to the redundancy of the DNA code, a known protein and its amino acid sequence can be coded by a potentially infinite number of DNA sequences. Furthermore, a protein with a known function can have a large number of subtly different protein relatives that perform substantially the same function. *See generally* MALACINSKI & FREIFELDER, *supra* note 1, at 68, 189-90.

65. *Amgen*, 927 F.2d at 1213 (citation omitted).

66. *Id.*; *see also In re Deuel*, 51 F.3d 1552, 1558-60 (Fed. Cir. 1995) (holding patent not

The *Amgen* case illustrates the unique difficulties inherent in biotechnology patents. Namely, the very nature of the protein and genetic properties make claiming all possible aspects of the invention nearly impossible. This, in turn, greatly reduces the patent protection of a patent and opens the door to a second party misappropriating the discovery.

1. Skill in the Prior Art

To circumvent this problem, some patent applicants argue that the preexisting skill in the prior art provides the information that is lacking in the disclosure. *Genentech, Inc. v. Novo Nordisk A/S*⁶⁷ concerned a patent that claimed a method of producing human growth hormone.⁶⁸ Although the specification did not adequately teach the method, the patentee argued “that the knowledge of one skilled in the art was sufficient to provide all of the missing information . . . [and] would enable the practice of the claimed method.”⁶⁹ The Federal Circuit held, however, that the patent was not enabled, because “[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.”⁷⁰ One of the major factors in the *Genentech* court’s opinion was the patent’s nondisclosure of starting materials or conditions under which the process could be carried out.⁷¹ This case and current Federal Circuit doctrine suggest that skill in the prior art will only be given limited value in enablement analysis.

2. Undue Experimentation

Intertwined with this question of skill in the prior art is the issue of “undue experimentation.” The *Wands* court clarified that some amount of experimentation could be tolerated in an enablement determination.⁷² Obviously, determining if

enabled when applicant claimed all permutations of a DNA sequence coding for a specific protein, but only disclosing the native sequence).

67. 108 F.3d 1361 (Fed. Cir. 1997).

68. Robert P. Taylor, *Section 112 Issues in Patent Infringement Cases*, in FIFTH ANNUAL INSTITUTE FOR INTELLECTUAL PROPERTY LAW 1999, *supra* note 36, at 33, 50.

69. *Genentech*, 108 F.3d at 1365.

70. *Id.* at 1366.

71. See Ben-Ami et al., *supra* note 36, at 574-76. But see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986) (holding that the specification need not disclose what is well known in the art); D. Benjamin Borson, *The Human Genome Projects: Patenting Human Genes and Biotechnology. Is the Human Genome Patentable?*, 35 IDEA 461, 487 (1995) (using the “inherency argument” that once a native DNA or part of the DNA is disclosed, the other forms of the DNA are “inherently disclosed” sufficiently to confer patentability).

72. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988) (stating that the key word is “undue” rather than “experimentation.”); *Johns Hopkins Univ. v. Cellpro, Inc.*, 152 F.3d 1342, 1361 (Fed. Cir. 1998) (finding no “undue experimentation” because challenger did not show that all of the disclosed alternatives did not work); *PPG Indus. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564-65 (Fed. Cir. 1996) (stating “harmless, inconsequential” errors that anybody skilled in the art would know how to fix do not make a patent fail on enablement grounds); see also *Hybritech*, 802 F.2d at 1384 (stating that a patent does not automatically fail the

experimentation is undue would depend upon who was doing the experimentation; a highly skilled and experienced scientist could probably achieve favorable scientific results more quickly than an undergraduate research assistant.

Interestingly, the hypothetical "person of ordinary skill" in enablement analysis is *not* assumed to have a complete knowledge of all of the prior art, whereas the counterpart "person of ordinary skill" in obviousness analysis is considered to have a perfect knowledge of the prior art.⁷³ This distinction puts a patent being attacked for lack of enablement at a disadvantage because it shifts the assumption of who is carrying out the experimentation toward the less-expert side of the spectrum. Therefore, a patentee defending an invention on enablement grounds is well served by establishing the "ordinary person skilled in the art" as having as much expertise as possible. Ultimately, the determination of whether an invention requires undue experimentation will boil down to an analysis using the *Wands* factors.⁷⁴

3. The Use of Specific Examples

One possible manner to ensure enablement is to include specific examples of a broadly claimed invention in the specification. The Federal Circuit has encouraged the use of examples, stating "it is irrelevant whether [the] teaching is provided through broad terminology or illustrative examples."⁷⁵ In *In re Goodman*,⁷⁶ the Federal Circuit held that a single example in the specification was not enough to enable one with ordinary skill in the art to overcome the problems with the invention.⁷⁷ There is no strict requirement for including examples in the specification, but specific examples might be the easiest or only method to adequately describe the invention. Therefore, as the unpredictability, complexity, and broadness of an invention increases, the need for examples also increases.

E. Special Concerns in Biotechnology Patents

The goal of an inventor applying for a patent is to claim as much material as broadly as possible.⁷⁸ Of course, if the patent claims too much it is susceptible to invalidation for lack of enablement.⁷⁹ When determining exactly how much to claim in a patent, the applicant must balance the risk of invalidation against the risk of claiming too narrowly and not adequately protecting the discovery. In a rapidly developing technology such as biotechnology, this balancing act becomes extremely difficult.

In a field such as biotechnology, the patent applicant must make the patent claims as broad as possible in order to anticipate future technical advances that would

enablement requirement if some experimentation is necessary).

73. See Winner, *supra* note 52, at 618.

74. See *In re Vaeck*, 947 F.2d 488, 495-96 (Fed. Cir. 1991) (stating that "undue experimentation" must be analyzed by looking at *Wands*-type factors).

75. *In re Wright*, 999 F.2d 1557, 1561-63 (Fed. Cir. 1993).

76. 11 F.3d 1046 (Fed. Cir. 1993).

77. *Id.* at 1050-53.

78. See MERGES ET AL., *supra* note 20, at 216.

79. See *supra* text accompanying notes 41-44.

otherwise make the patent useless.⁸⁰ Further, if inventors know the art is going to change quickly and make their patents useless, no economic incentive exists to develop research in the field.⁸¹ A classic example of this phenomenon in the biotechnology arena happens when a protein is developed through biochemical processes only to be preempted by a method of making the same protein using much cheaper and easier methods of molecular biology.⁸²

Assume, for example, a researcher develops a method of obtaining a highly purified extract of a commercially valuable protein such as insulin. The researcher can patent his biochemical method of protein production, but the process will become virtually useless if a subsequent party develops a method of expressing the same protein by inserting the DNA sequence into a bacterial expression vector.⁸³ Although both methods produce the same protein, the genetic expression method is much cheaper and more efficient at producing large volumes in industrial scales.⁸⁴ Therefore, the original patent will be useless unless its claims are broad enough to encompass all methods of producing the protein, including the subsequent genetic expression method.

Claiming all methods of producing the insulin, however, would probably be considered too broad and not enabled. Thus, the rapidly changing technology will have made the first patent's teachings obsolete, the resources put into the discovery will not be recouped, and subsequent researchers will have no economic incentive to develop similar protein purification methods for fear of similar subsequent technology preemption. This phenomenon also occurs frequently in instances where a discovery has the potential to apply to a number of species but has only been sufficiently enabled in one species, or if the discovery has potential in eukaryotic cells but has only been enabled in prokaryotic cells.⁸⁵

Compounding this problem is the date at which enablement analysis is done. Only the disclosure as of the date the patent was filed is pertinent, and all subsequent discoveries or data cannot be used to save an otherwise nonenabled discovery.⁸⁶ If a

80. See Winner, *supra* note 52, at 614 ("[I]f patent protection were . . . limited only to the specific embodiment by which the goal was reached, it would be so narrow as to be commercially meaningless.").

81. See Cannady, *supra* note 52, at 462.

82. Biochemical methods of protein production generally involve manipulations of the protein as a whole and of the amino acid sequence. Complicated methods and techniques exist with which to isolate and purify protein using basically mechanical means (for example, running the protein through specific filters and cleansing with chemical agents). Molecular biology methods usually involve manipulating the DNA sequence of the protein and devising genetic expression systems in bacteria in which the desired protein is expressed in a relatively pure form, with no need for mechanical methods of purification. See MALACINSKI & FREIFELDER, *supra* note 1, at 403-04, RIFKIN, *supra* note 2, at 18, 111-12 (describing this phenomenon in the vanilla industry).

83. See generally J. SAMBROOK ET AL., MOLECULAR CLONING: A LABORATORY MANUAL § 16.3 (2d ed. 1989) (discussing expression of protein from cloned genes).

84. See RIFKIN, *supra* note 2, at 18, 111-12.

85. See generally *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *Enzo Biochem, Inc. v. Calgene, Inc.*, 14 F. Supp. 2d 536 (D. Del. 1998), *aff'd in part and vacated in part* by 188 F.3d 1362 (Fed. Cir. 1999).

86. See *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1568 (Fed. Cir.

specification discloses the art for X and predicts the art will pertain to Y, subsequent discovery that the art pertains to Y is worthless because the discovery came subsequent to the original application date. Consequently, the inventor will only be given protection for what he can disclose at the time of the patent application.⁸⁷

Claiming broadly to protect against subsequent discovery preemption is virtually impossible because of this aspect of the enablement requirement. Inventors are faced with a truly difficult decision about when to file the patent application: early in order to protect the existing, limited discovery but risk being preempted by inadvertently teaching a competitor how to make a subsequent broad improvement, or waiting to get all the needed discoveries in order to enable the patent application broadly but risk being beaten to the filing date by a competitor.⁸⁸ Inventors are faced with a truly difficult decision about when to file the patent application. If they file early in order to protect the existing, limited discovery, they risk being preempted by inadvertently teaching a competitor how to make a subsequent broad improvement. However, if they wait to file until they get all of needed discoveries in order to enable the patent application broadly, they risk being beaten to the filing date by a competitor.

In the biotechnical arts, numerous balancing considerations exist for both the patent applicant and the courts. The patent applicant must attempt to claim as broadly as possible without claiming so much that her claim will be invalid for lack of enablement. Further, the researcher must decide if resources should be expended in developing a potential discovery by balancing the probability of sufficient patent protection to justify the expenditure against the probability the art will change so quickly that the patent will become obsolete.⁸⁹

The courts must balance the policy interest of encouraging research and development by giving inventors a limited monopoly in exchange for a quid pro quo against the policy against giving inventors too much protection by allowing extensively broad claims. If the judicial balance shifts too far on either side of the spectrum, a chilling effect in research and development will occur. If the courts protect too much, no incentive will exist to develop the art in the broad claim, because the original inventor will receive all economic benefits from a second party's subsequent work. If the court protects too little, the original inventor will have no incentive to produce the original discovery, because the lack of patent protection will not allow him to recoup his investment. Both the inventor and the courts have an extremely delicate balancing act that must be performed with countless subtle factors. This balancing act is particularly difficult in the unpredictable art of biotechnology.

1990) ("Merely because purer and more potent forms of the . . . compound might be produced using later-discovered technology does not necessarily mean that the . . . patent specification did not provide sufficient enabling disclosures as of the filing date of the application."); Taylor, *supra* note 68, at 51-52.

87. See *supra* text accompanying note 84.

88. See Cannady, *supra* note 52, at 475-76.

89. *Id.*

II. ANTISENSE TECHNOLOGY

In order to understand antisense technology, one must have a basic grasp of fundamental biology. DNA is present in all living cells and provides a set of instructions for the cell's machinery to use in carrying out cellular processes.⁹⁰ Of particular importance, the DNA code instructs the cell how to assemble amino acids to form the cell's various proteins.⁹¹ Antisense technology provides a method to block expression of certain unwanted genes by blocking this process.⁹²

A. Basic Science

DNA is made up of subunits called nucleotides of which there are only four: adenine (A), cytosine (C), guanine (G), and thymine (T).⁹³ A DNA molecule is made up of two strands of these nucleotides that are complementary to each other. A binds opposite to T and G binds opposite to C.⁹⁴ Of the two strands, only one strand known as the "sense" strand actually directs the cellular machinery.⁹⁵ The other strand is not read by the cellular machinery and is known as the "antisense" strand.⁹⁶ The antisense strand merely binds to the sense strand to make a stable molecule.⁹⁷ In order for the cellular machinery to read the instructions on the sense strand, the antisense strand must be temporarily removed to allow the cellular machinery (an enzyme known as RNA polymerase) access to read the code. If the antisense strand remains bound, the protein cannot be constructed because the antisense strand blocks the reading of the sense strand's code.⁹⁸ Antisense technology is based upon this basic concept.

To understand the particular mechanism for blocking the sense strand, the process of protein formation must be examined. In normal protein production, the RNA polymerase temporarily breaks apart the two strands and reads the nucleotide sequence on the sense strand. The RNA polymerase makes a strand of messenger RNA ("mRNA") that is complementary to the sense strand.⁹⁹ Since it is complementary, the mRNA strand is basically the same as the recently unbound antisense strand, with the minor difference of uracil (U) being used in place of T.¹⁰⁰ The RNA polymerase begins reading at a place known as a promoter and ends at a place known as a terminator. When the RNA polymerase has finished the process, the DNA rebinds, and the DNA, in its original bound form, remains in addition to the new mRNA strand that is basically the same sequence as the original antisense

90. See, e.g., MALACINSKI & FREIFELDER, *supra* note 1, at 39-40.

91. *Id.* at 187-99.

92. *Id.* at 182-83, 429.

93. *Id.* at 27.

94. *Id.* at 39-46.

95. *Id.* at 164.

96. *Id.* at 182.

97. The antisense strand does play an important role in the replication of DNA during cell division but, for the purposes of protein production, does not play any "instruction giving" role. *Id.* at 131-33, 163-74.

98. *Id.* at 174, 182-83.

99. *Id.* at 174-80.

100. *Id.*

strand.¹⁰¹ This first step of protein formation is known as transcription.

The second step in protein formation is known as translation. In translation, the mRNA strand formed from transcription is read by a second cellular machine (known as the ribosome).¹⁰² The ribosome translates the chain of nucleotides into a chain of amino acids to form the protein (amino acids are the subunits of protein much like nucleotides are the subunits of DNA and RNA).¹⁰³ The ribosome adds amino acids to the growing chain by following the order of the mRNA's nucleotide sequence.¹⁰⁴ Each set of three nucleotides in an mRNA is a code for a particular amino acid. Therefore, if the mRNA reads "AGC" the ribosome would attach the amino acid that corresponds to that particular sequence (in this case, the AGC codes for the amino acid serine).¹⁰⁵

A few particularly important variations of this process occur between eukaryotic and prokaryotic cells.¹⁰⁶ In eukaryotic cells, the process is somewhat more advanced because the mRNA produced in transcription goes through an additional editing process before the ribosome translates it.¹⁰⁷ The eukaryotic mRNA is acted upon by cellular machinery and certain portions (known as introns) are excised from the mRNA.¹⁰⁸ This editing process does not occur in the less complex prokaryote cells.¹⁰⁹ Also, the prokaryote cell does not have a nuclear membrane, so the translation occurs at substantially the same time and place as transcription.¹¹⁰ In contrast, eukaryotic cells possess a nuclear membrane, so the mRNA has to be transported outside of the nucleus into the cytoplasm before the ribosome can translate the mRNA.¹¹¹

B. Antisense

Antisense technology blocks protein formation by introducing an additional piece of DNA into the cell.¹¹² This DNA corresponds to a particular gene that is intended to be blocked, but the DNA is inverted with respect to the original DNA.¹¹³ As long as the promoter region is the same for the original gene and the newly added inverted

101. *Id.*

102. NEIL A. CAMPBELL, *BIOLOGY* 325-31 (3d ed. 1993).

103. *Id.*

104. *Id.* at 321.

105. *Id.*

106. Prokaryotic cells are generally single celled bacteria that are very primitive in organization and function. Eukaryotic cells usually are organized as multicellular organisms, have a cell wall and multiple cellular organelles, and have much more complex mechanisms of metabolism. *Id.* at 121-23. Although the two types of cells are quite different, molecular biologists generally use prokaryote cells as subjects on which to experiment, and then extrapolate the findings to the more complex eucaryote cells. See MALACINSKI & FREIFELDER, *supra* note 1, at 13.

107. CAMPBELL, *supra* note 102, at 332-35.

108. *Id.* at 333-35

109. *Id.* at 332-33.

110. *Id.*

111. *Id.*

112. See MICHAEL R. CUMMINGS & WILLIAM S. KLUG, *CONCEPTS OF GENETICS* 538-39 (5th ed. 1997).

113. See *id.*

gene, the RNA polymerase will translate both pieces of DNA at the same time.¹¹⁴ However, because the new DNA is inverted, the antisense strand is translated instead of the sense strand.¹¹⁵ In effect, this newly introduced DNA has the same effect as if the RNA polymerase would have translated both strands of the original DNA.¹¹⁶ In addition to the mRNA produced in normal transcription, the newly inserted DNA produces its own mRNA.¹¹⁷ Just as the sense and antisense strands of the original DNA are complementary and bind to one another, the strand of original mRNA and the mRNA product from the newly introduced DNA are complementary.¹¹⁸ When the two pieces of mRNA bind to one another, the ribosome is unable to translate the protein, and expression of the gene is blocked.¹¹⁹ Thus, antisense technology blocks protein formation by introducing an extra antisense DNA into the cell, which binds to the original and obstructs the reading of the original DNA by RNA polymerase or the mRNA by the ribosome.¹²⁰

III. ENZO BIOCHEM V. CALGENE

Enzo Biochem, Inc. was the exclusive licensee of a patent claiming a method of controlling the function of any gene in any cell through genetic antisense.¹²¹ Calgene, Inc. obtained its own patent claiming antisense regulation of gene expression in plants.¹²² The Calgene patent was used in the development of Calgene's FLAVR SAVR tomato, which blocked the gene responsible for ripening and increased the shelf life of the tomato.¹²³ Enzo claimed that Calgene had infringed on its patents, which resulted in Calgene challenging the breadth of Enzo's claims for lack of enablement.¹²⁴ The district court held that Calgene had not infringed on Enzo's patent and that parts of Enzo's patents were invalid for lack of enablement.¹²⁵ The Federal

114. James A.H. Murray & Nigel Crockett, *Antisense Techniques: An Overview*, in RNA AND DNA 1, 27-28 (James A.H. Murray ed., 1992).

115. See CUMMINGS & KLUG, *supra* note 112, at 538.

116. *Id.*

117. See Murray & Crockett, *supra* note 114, at 5.

118. *Id.* at 4.

119. CUMMINGS & KLUG, *supra* note 112, at 538.

120. See Murray & Crockett, *supra* note 114, at 4-5, 28.

121. *Enzo Biochem, Inc. v. Calgene, Inc.*, 14 F. Supp. 2d 536, 542 (D. Del. 1998), *aff'd in part and vacated in part* by 188 F.3d 1362 (Fed. Cir. 1999).

122. *Id.*

123. See *id.* at 542.

124. *Id.* at 541.

125. The determination of noninfringement of the Enzo patents raises interesting issues about the doctrine of equivalents. The doctrine of equivalents allows a finding of infringement in cases where literal infringement is not found. In *Enzo*, the district court made a distinction between "inverted DNA" in the Enzo patent and "cDNA" in the Calgene patent. See *id.* at 557-58. Also, the court reasoned that since the plant (prokaryotic) mRNA contains introns, the antisense process is fundamentally different than in eukaryotic mRNA. *Id.* Scientifically, neither of these distinctions necessarily justify a finding that the Calgene patent does not infringe Enzo's patent under the doctrine of equivalents. Ultimately, since the Enzo patent was found invalid for lack of enablement, this mistake would not change the ultimate result of the litigation. The district court's doctrine of equivalents analysis in *Enzo*, however, provides an

Circuit affirmed the district court's decision.¹²⁶

A. The Patents

Enzo's '931¹²⁷ patent included claims for the general invention of antisense technology,¹²⁸ claims for the method of antisense regulation,¹²⁹ and claims for cells which possess antisense technology.¹³⁰ Although the Enzo patents claim antisense technology in both eukaryotic and prokaryotic cells, the Enzo patent application only provided specific examples of antisense technology with respect to four prokaryotic genes.¹³¹ The antisense technology worked well in these four examples, but worked poorly or not at all when attempted in other prokaryotic and eukaryotic genes.¹³² This difficulty in extrapolating the Enzo patent's teachings to other genes was the root of the problem with the patent and ultimately led to the lack of enablement finding by the district court.

The prosecution of the Enzo patent was replete with examples of extreme difficulty and unpredictability of the antisense technology. The scientist responsible for the Enzo patent, Dr. Masayouri Inouye, reported failure of antisense regulation in ten or twelve other prokaryotic genes.¹³³ Furthermore, the antisense regulation of the four genes given as examples in the patent specification was not always successful when

interesting application of the confusing doctrine.

126. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362 (Fed. Cir. 1999). The Federal Circuit did remand a portion of the district court's decision which pertained to Calgene's demand for attorney's fees. *Id.* at 1381. The remanded portion of the opinion is not pertinent to this Note.

127. U.S. Patent No. 5,190,931 (issued March 2, 1993).

128. Claim 1 of the '931 patent reads:

A prokaryotic or eukaryotic cell containing a nonnative DNA construct, which construct produces an RNA which regulates the function of a gene, said DNA construct containing the following operably linked DNA segments:

- (a) A transcriptional promoter segment;
- (b) A transcription termination segment;
- (c) A DNA segment;

whereby transcription of the DNA segment produces a ribonucleotide sequence which does not naturally occur in the cell, is complementary to a ribonucleotide sequence transcribed from said gene, and said nonnaturally occurring ribonucleotide sequence regulates the function of [the] gene.

Enzo, 14 F. Supp. 2d at 550.

129. Claim 3 of the '931 patent reads: "A method of regulating the function of a gene in a prokaryotic and eukaryotic cell which comprises introducing into said cell the DNA construct of claim 1." *Id.* at 553. These types of claims are known as "method claims." See Mark D. Janis, *Who's Afraid of Functional Claims? Reforming the Patent Law's § 112*, ¶6 *Jurisprudence*, 15 SANTA CLARA COMPUTER & HIGH TECH. L.J. 231, for a discussion of method claims.

130. *Enzo*, 14 F. Supp. 2d at 550.

131. The genes were *Escherichia coli* bacteria genes, specifically: outer membrane protein A, C, and lipoprotein. *Id.* at 545.

132. *Id.* at 546-47.

133. *Id.* at 545.

attempted in Inouye's lab.¹³⁴ Also, Inouye never successfully carried out antisense regulation on prokaryotic cells, despite numerous attempts.¹³⁵ Other scientists in the field reported extreme difficulty in successfully carrying out antisense regulation on numerous genes.¹³⁶ Perhaps most damning was the fact that during prosecution of the Enzo patent, Inouye applied for a grant from the National Institutes of Health in order to determine the likelihood of success of antisense regulation in eukaryotic cells.¹³⁷ The general scientific consensus was that antisense regulation could only be successful on a gene-by-gene basis requiring experimentation for each gene.¹³⁸ Inouye's original patent application was rejected ten times on nonenablement grounds before being granted.¹³⁹ For all of these reasons, the Enzo patent was particularly susceptible to nonenablement attack.

B. The Nonenablement Finding

Calgene argued that Enzo's patent claims were too broad to be enabled because to practice the patent beyond the examples given in the specification required "undue experimentation by individuals with extraordinary skill in the art."¹⁴⁰ The district court used the *Wands* factors analysis in determining that the Enzo patent was too broad and not enabled.¹⁴¹

One of the most crucial *Wands* factors analyzed was the skill of those in the art. Enzo argued that the extremely complicated nature of the art disclosed in the patent required an extremely high skill in the art in order to practice the patent.¹⁴² Enzo reasoned that "where technology is very complex, one person will rarely practice an invention outside of his or her specialty."¹⁴³

The district court decided that "ordinary skill" in this case was markedly less than what Enzo postulated.¹⁴⁴ The court determined that "ordinary skill" would be a "junior faculty member with one or two years of relevant experience or a postdoctoral scientist with several years of experience"¹⁴⁵ because this was the skill level of the majority of persons who carried out the research and experiments in antisense technology. The court was unwilling to allow Inouye to claim a higher "ordinary

134. *Id.*

135. *Id.*

136. *See, e.g.,* Stuart K. Kim & Barbara J. Wold, *Stable Reduction of Thymidine Kinase Activity in Cells Expressing High Levels of Anti-sense RNA*, 42 CELL 129 (1985).

137. *Enzo*, 14 F. Supp. 2d at 548.

138. Such case-by-case situations are not uncommon in biotechnology research due to the extremely complex mechanisms involved in cellular organisms. Mechanisms of gene expression can differ from cell to cell within one organism and from gene to gene within a particular cell. *See generally* MALACINSKI & FREIFELDER, *supra* note 1.

139. *Enzo*, 14 F. Supp. 2d at 547.

140. *Id.* at 566.

141. *Id.*

142. *See infra* Part III.C.2.b (discussing the role that "the level of ordinary skill in the art" has in enablement analysis).

143. *Enzo*, 14 F. Supp. 2d at 567.

144. *Id.*

145. *Id.*

skill" level than his own lab had used in developing the antisense technology.¹⁴⁶

Closely connected to this factor was the question of undue experimentation. Calgene pointed out all of the difficulty surrounding the Enzo patent prosecution and the difficulty that other scientists had in practicing the patent.¹⁴⁷ Enzo argued that some amount of experimentation is allowed under *Wands*, and that every possible method for using antisense in every gene is not needed because the preexisting knowledge in the art and the natural progression of the field would enable subsequent users to use the antisense technology for all other genes.¹⁴⁸ However, the court followed its reasoning in *Genentech, Inc. v. Novo Nordisk A/S*¹⁴⁹ and held that the specification must enable the patent, not the prior skill in the art.¹⁵⁰ The large amount of evidence illustrating extreme difficulty in practicing Enzo's patent supported the court's decision.

The court further analyzed the *Wands* factors and determined that direction and guidance in the specification were inadequate, the examples given were too narrow and unreliable, the art was highly unpredictable, and the breadth of the claims at issue were much broader than the specifications.¹⁵¹ Under the *Wands* analysis, the district court held the Enzo patent invalid for lack of enablement,¹⁵² and the Federal Circuit subsequently affirmed that decision.¹⁵³

C. Problems of Enablement That Exist in the Wake of Enzo

Enzo was faced with the basic dilemma that faces all patent seekers in the unpredictable arts. In order for the money spent developing the patent to be justified, the patent must make sufficiently broad claims to cover trivial subsequent discoveries in the art.¹⁵⁴ However, Enzo erred too far on the side of protection and lost its patent for lack of enablement. The evidence surrounding this particular case did suggest that Enzo was claiming much more than it actually deserved.¹⁵⁵ However, the decision is important because it signals the Federal Circuit's continued application of its trend to give teeth to the enablement requirement.¹⁵⁶

146. *Id.*

147. Evidence of post-filing discoveries is only allowed in specific situations. Using post-filing discoveries is allowed to show a claim cannot be practiced without undue experimentation, but an inventor cannot use post-filing discoveries to show that his patent claim is enabled. *In re Hogan*, 559 F.2d 595, 605 (C.C.P.A. 1977). Therefore, Enzo was not allowed to save the claim by showing Inouye successfully used antisense technology in eukaryotic cells after he filed for the patent, but Calgene was allowed to use post-filing evidence to show lack of enablement. *Enzo*, 14 F. Supp. 2d at 568.

148. *Id.* at 566.

149. 108 F.3d 1361 (Fed. Cir. 1997); *see supra* text accompanying notes 67-71.

150. *Enzo*, 14 F. Supp. 2d at 566.

151. *Id.* at 568.

152. *Id.* at 566-69.

153. *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1377 (Fed. Cir. 1999).

154. *See supra* text accompanying notes 78-81.

155. *Enzo*, 14 F. Supp. 2d 536.

156. *See generally*, Cannady, *supra* note 52 (arguing that *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993), signals the enablement requirement has become quite strong).

1. The Increasing Trend of Adding Bite to the Enablement Requirement

The Federal Circuit has established a trend in which the enablement requirement has become increasingly stringent.¹⁵⁷ In particular, the Federal Circuit gave the enablement requirement real bite in *In re Wright*.¹⁵⁸ The Wright patents claimed vaccines that would work against RNA viruses.¹⁵⁹ The patents claimed a specific vaccine that had been developed, as well as general vaccines of the type.¹⁶⁰ The Federal Circuit held the broader claims involving the general vaccines invalid for lack of enablement.¹⁶¹ In doing so, some commentators have argued that the “the court elevated the standard for an enabling disclosure from a reasonable expectation of success to a demonstrated success . . . [and] could be interpreted as holding that the specification must enable one of ordinary skill in the art to practice the invention without any experimentation, rather than without undue experimentation.”¹⁶²

Essentially, the Federal Circuit has done this in *Enzo* as well. Although the *Enzo* court supports its holding with ample evidence of extreme difficulty in practicing the broad patents, the decision could be interpreted as saying that a patent will only be granted in the unpredictable arts if the patentee has successfully practiced every part of the claimed invention. Although this is not necessarily an incorrect standard to set forth, the decision does signal that the enablement standard has become increasingly stringent.

2. The Obviousness-Enablement Dichotomy Problem

This rise in the strength of the enablement requirement raises a few other important problems. The patent applicant in the unpredictable arts is faced with internal tension within the structure of the patent law.¹⁶³ The patent must be nonobvious to receive the patent. The nonobviousness requirement of patent law requires that the invention contain a truly inventive step, and that it be more than just a trivial extension of the prior art.¹⁶⁴ The nonobviousness requirement is in tension with the enablement requirement.

157. See generally *id.* at 473; Eisenberg & Merges, *supra* note 10, at 37-44.

158. 999 F.2d 1557 (Fed. Cir. 1993).

159. Cannady, *supra* note 52, at 455.

160. *In re Wright*, 999 F.2d at 1560.

161. *Id.*

162. Cannady, *supra* note 52, at 473.

163. *Id.* at 461-62.

164. The Supreme Court outlined the requirements of enablement in the quintessential case, *Graham v. John Deere Co.*, 383 U.S. 1 (1966). The court stated that the invention must be the work of an inventor and not just a skilled mechanic. *Id.* at 11. The court also established secondary considerations used to analyze obviousness: commercial success, long-felt but unsolved need, failure of others, copying, and unexpected results. *Id.* at 17-18; see also *Greenwood v. Haitori Seiko Co.*, 900 F.2d 238, 241 (Fed. Cir. 1990).

a. Predictability

To pass the nonobviousness hurdle, the patent applicant must portray the invention as being unpredictable or risk a finding that the invention be considered obvious with respect to the prior art. However, after passing the nonobviousness requirement the patent applicant must immediately redirect the portrayal of her invention as predictable in order to pass the enablement requirement. The patent applicant must walk a tight rope of sorts, portraying the invention as unpredictable enough to make it nonobvious, but predictable enough to make it enabled. If the applicant errs too far in one direction she will fall off of the tight rope into patent-rejection abyss.

The unique nature of biotechnology makes the danger of falling off the rope especially high. Scientific research in general, and biotechnology in particular, is a field that naturally builds upon previous discoveries in the field.¹⁶⁵ It is virtually unheard of for a scientific discovery to arrive completely in a vacuum, independent of any prior art discoveries, and for the new discovery to be completely predictable and functioning with a high degree of consistency and dependability.¹⁶⁶ A much more likely scenario is for a basic discovery to come forth (the general idea of antisense regulation, for example) and that basic idea be expanded and promulgated by slow and deliberate experimentation (the extrapolation of a known method of antisense regulation in one gene to another gene or another species, for example). Therefore, the patent applicant in biotechnology generally has an extremely small window in which to characterize his invention as predictable or unpredictable.

Since the invention most likely is a continuation of a known prior art, the invention is already at risk of failing for obviousness. To avoid patent denial for obviousness, the applicant must immediately highlight the unpredictability of the art to portray his or her invention as a truly inventive step. But, since the nature of biotechnology is unpredictable, and the invention most likely will be the result of extended experimentation in a small area of the prior art, the invention is already at risk of failing the enablement requirement for lack of predictability. In order to avoid patent denial for lack of enablement, the applicant must highlight the predictability of his invention. This internal struggle inherent in patent-law doctrine leaves the biotechnology patent applicant a precariously small gap in which to fit.¹⁶⁷

b. Person of Ordinary Skill

A second tension exists between obviousness and enablement. Both requirements are subject to a "person of ordinary skill" measurement, but the persons of ordinary skill are considered to have different skills between the two requirements.¹⁶⁸ In obviousness, the person of ordinary skill is a hypothetical person having complete

165. As Isaac Newton once wrote: "If I have seen further it is by standing on ye shoulders of giants." Letter from Isaac Newton to Hooke (Feb. 5, 1675/6), in 1 THE CORRESPONDENCE OF ISAAC NEWTON, 1661-1675, at 4162 (H.W. Turnbull, F.R.S. ed., 1959).

166. Winner, *supra* note 52, at 613 ("The model of the lone scientist working by candlelight among his bubbling retorts to come across a sudden and unexpected discovery no one could have anticipated does not apply to modern innovation.").

167. See generally Cannady, *supra* note 52, at 461-62 (pointing out this dichotomy).

168. See *supra* text accompanying note 73.

and instant knowledge of every prior art development. As developments occur, this person is assumed to know of them immediately. This is the person to whom a patent applicant must show the new invention would not be obvious.¹⁶⁹ However, as pointed out in *Enzo*, the person of ordinary skill for enablement analysis is not assumed to have perfect knowledge of the prior art. Much to the contrary, the person of ordinary skill is assumed *not* to have perfect knowledge of the prior art but to be somebody who “thinks along the line of conventional wisdom in the art and is not one who undertakes to innovate.”¹⁷⁰ The patent applicant is held to a double standard of the “person with ordinary skill” measurement. The applicant must battle against the hypothetical supercomputer brain during obviousness analysis and then during enablement analysis must convince the courts the same “person” is not a bumbling simpleton. Again, this dichotomy within the patent law places the applicant for a biotechnology patent in a precarious situation.

3. The Need for Ad Hoc Analysis

The extreme complexity of biological systems makes enablement analysis nearly impossible to apply other than on a case-by-case basis. No general guidelines for patent-law enablement doctrine can be expounded because enablement is so deeply dependent on the particular nature of each and every patent, and each and every patent is so unlike all others. The *Wands* factors provide as much guidance as possible but still allow a lot of latitude to argue each case on an ad hoc basis. This complicated set of balancing factors and ad hoc examinations might be necessary in order to preserve the quid pro quo so crucial to patent-law policy and to ensure that the public is getting an adequate benefit in exchange for the inventor’s limited monopoly grant.

Of course, many areas of the law do not lend themselves well to easily applied general doctrines, and courts must make ad hoc balancing determinations frequently. However, the special problems inherent in the biotechnological arts make patents in the field particularly susceptible to patent invalidation.

CONCLUSION

Perhaps because of the very fact that biotechnology is so complex and unpredictable, the Federal Circuit should continue to add teeth to the enablement requirement to prevent inventors from claiming an entire area of technology that they have not sufficiently discovered. It was this idea of unfair taking that prompted the debate about patenting ESTs nearly ten years ago.¹⁷¹ Whatever the Federal Circuit decides to do with the enablement requirement in the future, a court must be aware of the problems specific to biotechnology. Before automatically invalidating a patent, a court should take into account the difficulties that patent applicants in biotechnology are forced to face.

The Federal Circuit furthered the trend it started in *In re Wright* and has elevated

169. Winner, *supra* note 52, at 618.

170. *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985).

171. *See supra* text accompanying notes 7-10.

the enablement standard from a reasonable expectation of success to an actual demonstration of success.¹⁷² In a field of biotechnology that is as complex and unpredictable as antisense technology, this is an acceptable approach. The best method of patent protection for such a field is to protect antisense technology on a gene-by-gene basis and force inventors to go through the leg work that successful antisense regulation requires. However, in a field that is not as unpredictable or complex, the enablement standard should be relaxed to what it was prior to *In re Wright* and *Enzo*. Further, if antisense technology becomes routine in the future, forcing each patent applicant to claim on a gene-by-gene basis would not achieve what the court wanted the *Enzo* decision to achieve, namely, for each inventor to solve the problems inherent in applying the technology to different genes. When no problems exist in applying the technology to a broad array of genes, the enablement requirement should be relaxed.

172. Cannady, *supra* note 52, at 473-74.