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THE TEST OF PRIMARY CLONING: A NEW APPROACH TO THE WRITTEN DESCRIPTION REQUIREMENT IN BIOTECHNOLOGICAL PATENTS†

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I. INTRODUCTION

To secure a patent for an invention, one of the most fundamental requirements is an adequate description of the invention in words.¹ Not only does the description help a patent examiner determine whether the invention meets the requirements for patentability,² but more importantly, it tells the world what has been invented as of the filing date of the patent application.³ It serves one of the main objectives of the patent system: fostering the exchange and sharing of ideas such that others may build and improve upon the creations of others.⁴ The written description requirement is codified in the patent

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2. Enzo II, 285 F.3d at 1022 (stating "[a]n adequate description is necessary for proper examination of an application").
4. Id.
statute and has been interpreted by courts in various ways throughout history within the context of specific technological fields.

In the biotechnology arena, the Court of Appeals for the Federal Circuit (CAFC) has interpreted the written description requirement in the context of claims to nucleic acid sequences on several occasions. Each decision seems to bring forth a new pronouncement regarding the sufficiency of a written description for such claims. This has lead to confusion in the legal community, even among members of the court as evidenced by a reversal, three months after the first decision, by the same panel of judges. Thus, it is currently not clear whether an inventor must demonstrate possession of the invention, list the sequence of the claimed nucleic acid, or support the claim by describing functional properties of the sequence correlated with other known attributes.

The conflicting decisions and lack of clear standards has led to debate in the legal community regarding how the written description requirement should be applied to nucleic acid sequence claims. This comment will explore the controversial CAFC decisions as well as the two sides of the debate. Then, noting that both sides of the debate have merit, this paper concludes with a proposal reconciling the sides by providing a novel test for nucleic acid sequence claims, dubbed the primary cloning test. The primary cloning test addresses the dual nature of nucleic acids as molecules amenable to scientific discovery and isolation from their natural sources, and, secondarily, as molecules of laboratory experimentation. This test is then applied to the Enzo patent currently pending before the district court on remand from the CAFC. The primary cloning test creates a new,

6. Enzo I, 285 F.3d at 1013, vacated by Enzo II, 296 F.3d at 1316.
7. Fiers v. Revel, 984 F.2d 1164, 1167 (Fed. Cir. 1993); but see Enzo II, 296 F.3d at 1330.
11. Enzo II, 296 F.3d at 1316.
bright-line criterion to guide consideration of the adequacy of the written description supporting nucleic acid sequence claims.

A. Some Basics of the Science Underlying the Biotechnology Industry

Before discussing the written description requirement as it relates to nucleic acid sequence claims, a basic review of the underlying science and its application to biotechnology is provided. The starting point for the modern biotechnology industry was the discovery that deoxyribonucleic acid (DNA) can be recombined in a way allowing for the inexpensive and efficient mass production of proteins encoded by the recombined DNA. DNA is the informational chemical found in each living cell that determines the physical characteristics and properties of that cell and provides the basis for transmission of heritable traits to progeny. The informational aspect of DNA is inherent in its chemical structure. Four different types of chemical building blocks known as nucleotides (adenine [A], guanine [G], cytosine [C] and thymine [T]) are linked together via a phosphate backbone. The now-famous DNA double helix structure consists of two complementary DNA strands paired together through chemical bonds between the nucleotides. The nucleotide A always pairs with T and the nucleotide G always pairs with C. The structure allows for the faithful copying of genetic information and transmission of copied information to progeny. DNA is divided into functional units called genes. Genes encode proteins that do the work of the cell. Only a small portion of DNA actually encodes proteins, the rest of the DNA molecule provides structural and other functional signals.  

13. See, e.g., STEPHEN S. HALL, INVISIBLE FRONTIERS, THE RACE TO SYNTHESIZE A HUMAN GENE (1987), (chronicling the early events in university labs, start-up biotechnology companies and the pharmaceutical company, Eli Lilly & Co., to generate recombinant human insulin); MOLECULAR CELL BIOLOGY 244–46 (Harvey Lodish et al. eds., 2000).
15. Id. at 100–01.
16. Id. at 101–03.
17. Id. at 103.
18. Id.
19. Id. at 5.
20. LODISH, supra note 13, at 3–5.
21. Id.
synthesis of proteins requires the generation of an intermediate molecule, messenger ribonucleic acid (mRNA). Messenger RNA is a single stranded copy of the protein-coding part of the DNA from which it is derived and the nucleotide sequence of the mRNA determines the protein that will be made.\(^{23}\)

A key discovery enabling the birth of the biotechnology industry was that stable DNA copies of mRNA, called complementary DNA (cDNA), can be made using certain proteins derived from viruses.\(^{24}\) When cDNA is recombined (or cloned) in a specialized DNA molecule known as a vector and inserted into a host cell, the host cell is transformed into a living factory for production of the protein encoded by the particular cDNA.\(^{25}\) This is the essence of the modern biotechnology field that produces recombinant proteins, such as insulin and growth hormone, for therapeutic use.\(^{26}\)

It would be impossible to create recombinant vectors containing cloned cDNA without methods to “see” the DNA, isolate it and manipulate it in the laboratory. Many such methods are based upon another key discovery pertaining to a chemical property of DNA.\(^{27}\) This property is that the two strands of the double helix can be separated from each other temporarily and then be brought back together again.\(^{28}\) DNA separation occurs naturally in the cell\(^{29}\) and this property of DNA has been exploited experimentally as described below.

In the laboratory, any two complementary single-stranded nucleic acid chains, whether composed of DNA or RNA, can be induced to pair with one another through the chemical bonding of A’s with T’s\(^{30}\) and C’s with G’s in a reaction known as hybridization.\(^{31}\) Thus, an investigator can prepare a labeled (usually using a radioactive or fluorescent tag) nucleic acid probe and follow it during

\(^{23}\) LODISH, supra note 13, at 5.

\(^{24}\) See, e.g., HALL, supra note 13, at 18–19; LODISH, supra note 13, at 219–21.

\(^{25}\) LODISH, supra note 13, at 227.

\(^{26}\) See, e.g., HALL, supra note 13, at 18–19.

\(^{27}\) See, e.g., MOLECULAR BIOLOGY OF THE CELL 188–96 (Bruce Alberts et al. eds., 2d ed. 1989).

\(^{28}\) Id. at 188.

\(^{29}\) The strands of DNA separate in the cell during the process of DNA replication in which a complete copy of all nuclear DNA (in the form of chromosomes) is made for passage to a new daughter cell. Likewise, the strands of DNA separate during the process of RNA synthesis, including mRNA synthesis. See, e.g., ALBERTS, supra note 27, at 514–527.

\(^{30}\) In the case of RNA, thymine is replaced by uracil, so adenine bonds with uracil. See, e.g., ALBERTS, supra note 27, at 98.

\(^{31}\) See, e.g., ALBERTS, supra note 27, at 188.
an experiment. The probe is a single stranded nucleic sequence that hybridizes to a DNA or RNA strand that is its exact partner for pairing between the nucleotides, also known as the complementary strand. As an example, if the target DNA sequence is ACGTGC, then the probe sequence that will hybridize to the target is TGCACG. Such hybridization reactions between probe and target nucleic acid sequences have been exploited to study a number of cellular and biochemical processes as well as to clone genes and to perform numerous experimental procedures.

In addition, it is known that experimental parameters, such as temperature and salt concentration, can be altered to lessen the fidelity of pairing between nucleotides. If the target DNA sequence is ACGTGC as in the hypothetical example above, but the probe sequence contains a one base mismatch and reads TGTACG, it can still be induced to hybridize to the target by simply modifying the experimental parameters. This has been exploited to clone genes of distantly related organisms using the first cloned member of a gene family as a probe to isolate other members of the family even though the gene sequences are non-identical.

Today, recombinant DNA technology and the resulting biotechnology industry have grown to encompass a wide array of activities including the creation of new research tools, diagnostic tests, agricultural products, veterinary products and human therapeutics. Therefore, a precise definition of biotechnology for the purpose of discussion is required. Here, biotechnology takes a very limited definition and means solely the cloning and manipulation of nucleic acid molecules. This definition is chosen because the cases discussed at length in this paper pertain to patents with claims to nucleic acid sequences and because claims to nucleic acid sequences continue to dominate the scientific and legal interface.

32. Id. at 189.
33. Id. at 188–96.
34. Id. at 188–93.
35. Id. at 191–92.
36. Nucleic acids refer to both DNA and RNA molecules, both of which are linear strings, or polymers, of nucleotides. A nucleotide consists of a nitrogen containing base linked to a sugar and one or more phosphate groups. RNA differs from DNA in that the sugar phosphate backbone contains ribose instead of deoxyribose, it contains the base uracil instead of thymine, and it is single-stranded instead of double stranded. See, e.g., ALBERTS, supra note 27, at 98.
II. DEFINING THE WRITTEN DESCRIPTION CONTROVERSY IN
BIOTECHNOLOGICAL (NUCLEIC ACID SEQUENCE) PATENTS

A. The Written Description Requirement in Biotechnological
Patents

The patent statute states the written description requirement as
follows:

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. 37

The courts have interpreted this language in different ways over
time. Before the advent of biotechnology, the written description
requirement was first ancillary to enablement—it was to enable one
skilled in the art to make and use the invention. 38 The written
description also served to put the public in possession of the
invention. 39 Later, the written description was employed in the
context of claims added or amended after filing the application. 40 The
inventor was limited to adding or amending claims to the extent they
were supported by the written description of the originally filed
application. 41 Thus, the written description served as notice of what
the inventor possessed at the time of filing and therefore prevented
overreaching, that is, claiming subject matter that the inventor did not
actually invent. 42

In the context of biotechnology, one of the early cases that
examined the written description requirement was Fiers v. Revel. 43
This case was a three-way priority contest pertaining to DNA
encoding human beta-interferon. Revel’s patent application disclosed
methods for isolating DNA and mRNA coding for beta-interferon, but
did not disclose a complete beta-interferon DNA sequence. 44 The

39. Id.
41. Id.
42. Id. at 995–96.
43. 984 F.2d 1164 (Fed. Cir. 1993).
44. Id. at 1167.
court found the written description inadequate to support a claim to the entire coding sequence\(^{45}\) using the test of whether the disclosure conveys to one skilled in the art that the inventor possessed the invention claimed.\(^{46}\) In addition, the court enunciated written description guidelines adequate for claiming DNA sequences explaining that "what is required is a description of the DNA itself."\(^{47}\) A description of the DNA is shown by reciting a "structure, formula, chemical name, or physical properties,"\(^{48}\) not merely by disclosing "a plan, for obtaining the DNA."\(^{49}\)

The next case to address written description in the context of biotechnological patents was *Regents of the University of California. v. Eli Lilly & Co.*, which also involved a priority contest over DNA sequences.\(^{50}\) The University of California (U.C.) alleged that Lilly infringed a patent claiming cDNA encoding human insulin.\(^{51}\) The patent specification described a method for isolating and cloning human insulin cDNA, along with the amino acid sequence of the insulin protein, but did not disclose any sequences corresponding to the human insulin cDNA, the claimed invention.\(^{52}\) Citing the language in *Fiers* that DNA is described by reciting a "structure, formula, chemical name, or physical properties,"\(^{53}\) the court held that the claim was invalid for failing to provide an adequate written description.\(^{54}\) The disclosure was found to be a general method for obtaining the cDNA, not a description of the cDNA itself.\(^{55}\)

Furthermore, U.C. contended that the disclosure was adequate because additional claims broadly covered vertebrate insulin cDNA and mammalian insulin cDNA, and the sequence of rat insulin cDNA, a species within both vertebrate and mammalian genera, was provided.\(^{56}\) The court rejected this argument finding that a sequence to one member of a genus, without more, did not describe the entire

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45. *Id.* at 1171.
46. *Id.* at 1170.
47. *Id.*
48. *Id.* at 1171.
49. *Fiers*, 984 F.2d at 1171.
50. 119 F.3d 1559 (Fed. Cir. 1997).
51. *Id.* at 1562–63.
52. *Id.* at 1567.
53. *Fiers*, 984 F.2d at 1171.
55. *Id.* at 1567.
56. *Id.*
The entire genus was described only by function, in other words, the genus was described by what it did and not by what it was. Thus, the court held these claims invalid as well.

B. The Enzo I and Enzo II Decisions of 2002 Demonstrate Judicial Confusion over the Written Description Requirement in Biotechnological Patents.

The Lilly decision discussed above generated much debate in the legal community with some commentators arguing that it imposed a heightened requirement upon biotechnological patents that would hinder innovation and hurt the industry while others argued that Lilly was correctly decided and would prevent overreaching by inventors thereby fostering the growth of the industry. These points are discussed in greater detail below. But perhaps the most unfortunate aspect of the Lilly decision was that while it clearly signaled the importance of supporting nucleic acid claims with an adequate written description, it failed to articulate clear and definite standards by which to do so. Nowhere is this more evident than in the 2002 Enzo decisions in which the CAFC initially found the written description supporting claims to DNA sequences inadequate in Enzo I, and then, upon rehearing, reversed the decision in Enzo II.

The patent at issue in the Enzo decisions was directed to DNA sequences that distinguish the bacterial causative agent of gonorrhea, Neisseria gonorrhoeae, from its closely related cousin, Neisseria meningitides, based on the ability of the DNA of the invention to preferentially hybridize to the genome of N. gonorrhoeae. Three of the cloned DNA sequences belonging to the claimed genus were deposited in the public repository, the American Type Culture Collection (ATCC). None of the DNA molecules of the invention

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57. Id. at 1568.
58. Id.
59. Id. at 1570.
60. See, e.g., Mueller, supra note 10, at 615; Rai, supra note 10, at 827.
61. See, e.g., Sampson, supra note 10, at 1236.
63. Enzo II, 296 F.3d at 1316.
64. '659 patent, supra note 11.
65. The deposit of biological materials for patent purposes is governed by regulations set forth at 37 C.F.R. §§ 1.801-1.809; ATCC is a global, nonprofit bioresource center established in 1925 and located near Washington D.C. It maintains stocks of all types of biological materials received from scientists around the world. These include recombinant DNA clones for genes from different species and other DNA sequences including probes and vectors, cell lines from
were described by their sequence. Thus, citing Lilly, the defendants contended that the patent was invalid for lack of an adequate written description for the claimed DNA sequences.

The patentee presented three main arguments to support the contention that the claimed DNA sequences were adequately described, all of which were initially rejected by the CAFC. The first argument was that the preferential hybridization ascribed to the claimed DNA sequences was a binding affinity (referring to the strength of the chemical interaction between two molecules), and as such, satisfied the PTO Written Description Guidelines which provide that the written description requirement for some biomolecules may be met by providing "examples of identifying characteristics including a sequence, structure, binding affinity, binding specificity, molecular weight and length." Second, Enzo contended that describing DNA by hybridization to a target DNA sequence is an adequate written description since DNA hybridization is a specific chemical interaction occurring between complementary sequences. The court was unconvinced with both of these arguments and stated that hybridization of one DNA molecule to another describes what the DNA does, not what it is, and is therefore stating the function of the DNA and is an inadequate written description after Lilly.

The final argument in support of the '659 patent was that possession was shown by an actual reduction to practice and by deposit of three bacterial strains containing cloned DNA sequences of the invention at ATCC thereby satisfying a primary purpose of the written description requirement. The court agreed that possession of the invention had been shown, but disagreed that mere demonstration of possession was sufficient to satisfy the written description

numerous organisms, including hundreds of human tumor cell lines and embryonic stem cell lines, microorganisms, plants and other biological materials. These materials are provided upon request to individuals in universities and private industry as well as governments around the world. ATCC personnel also perform research, provide technical services and educational programs with the goal of advancing scientific knowledge.

See http://www.atcc.org/About/AboutATCC.cfm (last visited Nov. 3, 2003).

66. '659 patent, supra note 11.
67. Enzo I, 285 F.3d at 1018.
68. Id. at 1017–19.
69. Id. at 1017.
70. Written Description Guidelines, 66 Fed. Reg. at 1110 n.42.
71. Enzo I, 285 F.3d at 1018.
72. Id. at 1018–19.
73. Id. at 1022–23.
requirement because there was insufficient distinguishing information about the sequences to support the claims.  

Following this decision, Enzo successfully petitioned for a rehearing, which took place in front of the same three-judge panel. In a reversal written by Judge Lourie (who also authored Enzo I), the CAFC held this time that a functional description of DNA, if coupled with a known or disclosed correlation between structure and function, could satisfy the written description requirement. Moreover, a deposit of biological materials in a public repository could satisfy the written description requirement, but not because it shows possession of the invention.

What rationale supports the court’s reversal? First, the court reexamined the Lilly decision in view of the PTO Written Description Guidelines and concluded that while a functional description of DNA in the Lilly case was not an adequate written description, it is incorrect to conclude that all functional descriptions of DNA are inadequate written descriptions (emphasis added). This is true because, according to the PTO Written Description Guidelines, the written description requirement can be met by disclosing sufficiently detailed identifying characteristics including chemical properties or functional characteristics when coupled with a known or disclosed correlation between structure and function. The court was particularly persuaded in adopting the structure-function correlation as a means of satisfying the written description requirement by the fact that the PTO would find a functional claim to an “isolated antibody capable of binding to antigen X” to be an adequate written description. In the antibody case, the claim describes what the antibody does but not what it is since it does not list the amino acid sequence. The written description is sufficient for the antibody, even though there is no amino acid sequence given for the antibody, because the structural characteristics of the five classes of antibodies are well defined, as are the functional characteristics of antibody binding, and antibody technology is well developed and mature. Thus, the court expressly adopted the PTO Written Description

74. Id. at 1021-22.
76. Id. at 1324–25.
77. Id. at 1325, 1329–30.
78. Id. at 1324.
79. Id. (citing Written Description Guidelines, 66 Fed. Reg. at 1106).
80. Id.
81. Enzo II, 296 F.3d at 1324.
Guidelines on this point and noted that if the preferential binding of the DNA sequences of the '659 patent to the \textit{N. gonorrhoeae} genome were correlated with a sufficiently known or disclosed structure, then the functional claim to such DNA sequences would be valid.\textsuperscript{82} This issue was remanded to the lower court.\textsuperscript{83}

Next, the court explained its rationale for holding that deposits could fulfill the written description requirement.\textsuperscript{84} The court acknowledged the inherent difficulties in adequately describing unique biological materials and determined that if such materials were deposited in a public repository, then one skilled in the art would be able to obtain the materials and literally see the scope of the invention (here, by sequencing the DNA of the claimed invention) thereby satisfying the written description requirement.\textsuperscript{85}

Finally, the court made an important distinction between the depositing of materials to satisfy the written description requirement and the depositing of materials or actual reduction to practice to show possession to satisfy the written description requirement.\textsuperscript{86} The court reiterated its prior holding that showing possession alone does not satisfy the written description requirement.\textsuperscript{87} The written description requirement "is the quid pro quo of the patent system; the public must receive meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time."\textsuperscript{88}

In summary, although the court in \textit{Enzo II} resolved the issues of whether some functional descriptions of DNA as well as deposits of biological materials in a public repository could satisfy the written description requirement, other issues were left for determination by the district court on remand creating further uncertainty for the foreseeable future. The most important of these issues is whether the hybridization function of DNA is correlated with a known structure of DNA in a manner sufficient to satisfy the written description requirement.\textsuperscript{89} Since the CAFC adopted the PTO Written Description Guidelines on this point, the district court's determination of this factual inquiry will likely be determinative.

\textsuperscript{82.} \textit{Id.} at 1324-25.
\textsuperscript{83.} \textit{Id.} at 1327.
\textsuperscript{84.} \textit{Id.} at 1325.
\textsuperscript{85.} \textit{Id.} at 1326.
\textsuperscript{86.} \textit{Id.} at 1329.
\textsuperscript{87.} \textit{Enzo II}, 296 F.3d at 1330.
\textsuperscript{88.} \textit{Id.}
\textsuperscript{89.} \textit{Id.} at 1327-28.
C. The View That the Written Description Requirement Should Be Broadly Interpreted.

After the Lilly decision, many commentators viewed the CAFC's holding as creating a new and heightened written description standard pertaining solely to biotechnological inventions. The assertion was that a required demonstration of physical possession would chill the development of new products and processes in the field.

The rationale is explained as follows. Patent law has always provided protection for alternative embodiments or variants of an invention that are not expressly described in the patent. This rewards inventors with protection for the full scope of their inventions and protects their rights by preventing competitors from avoiding patent infringement by simply making minor changes to the claimed invention. Thus, it is contended that a narrow written description requirement results in an inability to claim alternative embodiments thereby limiting the scope of patent protection. This chills investment in research because there is less incentive to invest in research when the scope of patent protection is limited. While this is a rational and meritorious argument, it fails to address the problem of overreaching inventors. This is the chief argument of the proponents of a narrow written description as explained below.

D. The View That the Written Description Requirement Should Be Narrowly Interpreted.

The narrow written description proponents contend that limiting nucleic acid sequence claims to those supported by a specific listing of the sequence comports with patent policy and fosters investment in basic research. One commentator applauded the Lilly decision stating that "any alternative approach to patenting genes, cDNAs, or mRNAs other than disclosing exact nucleotide sequences risks granting overly broad patent rights to a single inventor."

The rationale for this position is that due to the high degree of sequence similarity between related species, inventors can merely

90. See, e.g. Mueller, supra note 10 at 649; Rai, supra note 10, at 834.
91. Mueller, supra note 10, at 650.
92. Id. at 651.
93. Id.
94. Id.
95. Id.
96. See, e.g., Sampson, supra note 10, at 1261.
97. Id. at 1260.
clone and sequence a gene from one species and then claim the homologous gene from all related species, which is precisely what U.C. did in the patent at issue in *Lilly*. Without a requirement for listing the exact nucleotide sequence of the claimed DNA, inventors "could receive patent rights to sequences of which they have no knowledge, in organisms with which they have never worked." Furthermore, inventors could claim rights to naturally occurring single-nucleotide variants within a single species, also known as single-nucleotide polymorphisms, and other gene variants known as alleles and isoforms. Ultimately, this would lead to "nucleotide sequence claims becoming a Pandora's box that the patent law is unable to control."

Some commentators also argue that narrow patent rights to DNA sequences foster investment in research. The idea is that companies are encouraged to invest time and resources in cloning homologous genes and genes encoding protein variants which may prove more clinically useful than original isolates if the patent field is still open. While this may be true, the argument does not effectively deal with the contention of the broad written description proponents that narrow claims encourage companies to design around existing patents by slightly modifying DNA sequences subject to patent protection. Such practices could easily undermine the value of the original patent with detrimental consequences to the biotechnology industry. This is because biotechnology is particularly dependent upon strong patent protection due to the lengthy and costly product development process and the associated high risk of failure. This is especially true for therapeutic products.

An additional argument in the written description debate centers on the impact it will have on the number of patent holders in a given

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98. *Id.* at 1260–61.
99. *Id.*
100. *Id.* at 1260.
101. See *id.* (explaining how these variants are essentially the same gene that code for essentially the same protein with identical or similar properties and that single nucleotide variations in genes among individuals give rise to the diversity seen among members of the same species).
102. *Id.* at 1261.
103. See, e.g., *id.*
104. *Id.*
field. It is the consensus that broad patent claims limit the number of patent owners and narrow patent claims expand the number of patent holders. The dispute, then, revolves around whether it is best for the biotechnology industry to have many different patent holders or few.

The proponents of narrow patent claims contend that it is undesirable to have a situation where only a few patent holders control a field.\textsuperscript{107} This is because of the potential for one or a few patentees to extract exorbitant licensing fees, secure rights to the fruits of future research or even close off entire fields of research to competitors.\textsuperscript{108}

But the alternative situation that would occur with narrow patent claims seems equally unattractive. In this situation, there is a proliferation and fragmentation of patent rights with the net result that multiple entities end up owning small pieces of the intellectual property that cover a final product.\textsuperscript{109} Such a situation is particularly problematic when rights are granted to multiple entities covering early stage basic research,\textsuperscript{110} the category of research into which DNA sequence claims fit.\textsuperscript{111} The problem, deemed the "tragedy of the anti-commons,"\textsuperscript{112} is that multiple owners of the property each have a right to exclude others while no one has an effective privilege of use.\textsuperscript{113}

Then, companies seeking to develop products must secure multiple licenses from multiple entities, each carrying an associated transaction cost.\textsuperscript{114} Ultimately, each license represents an obstacle that the developer of a product must overcome, along with a transaction cost that will be passed on to the consumer, and the net

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\textsuperscript{107} See Penhoet, \textit{supra} note 105, at 24–25.
\textsuperscript{108} AGRAWAL, \textit{supra} note 106, at 33.
\textsuperscript{109} Rai, \textit{supra} note 10, at 839–40.
\textsuperscript{111} In general, DNA sequences are not stand-alone commercial products, with the exception of the small and highly specialized research products market. To date, DNA sequences have been used commercially in processes to produce therapeutic proteins and in diagnostic tests. In both these situations, the claimed DNA is but one part of the product, and in the case of therapeutic proteins, is not part of the product at all, but rather a part of the manufacturing process. Even in the field of gene therapy, which envisions using DNA as a therapeutic agent, the DNA must be combined with a delivery vehicle to make the final product. Since the discovery and cloning of DNA occurs at the beginning of the research and development process, and since the DNA is rarely a stand-alone commercial product, DNA sequences are more properly characterized as the fruits of early stage research as opposed to late stage product development.
\textsuperscript{112} Heller & Eisenberg, \textit{supra} note 110, at 698.
\textsuperscript{113} \textit{Id}.
\textsuperscript{114} Rai, \textit{supra} note 10, at 839–40.
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effect is a slowing of new products entering the market place at an increased cost.\textsuperscript{115}

In considering the arguments made above, it is apparent that each side has merit. The question then is how to reconcile the opposing viewpoints in a manner that preserves the traditional objectives of patent law—to encourage the creation and sharing of new inventions for the public good. One way is to adopt a new test, the primary cloning test, explained further below.

III. PROPOSAL: A PRIMARY CLONING TEST FOR APPLICATION OF THE WRITTEN DESCRIPTION REQUIREMENT TO NUCLEIC ACID SEQUENCE CLAIMS

One of the considerations absent from the debate over the written description requirement for nucleic acid sequence claims is the dual nature of DNA and other nucleic acids. First, they are molecules subject to discovery and isolation from natural (or primary) biological sources, and then following isolation or cloning, they become experimental molecules subject to endless manipulation in the laboratory. It is in the context of nucleic acid sequence claims to molecules that have never before been isolated and cloned from a primary source that a narrow interpretation of the written description requirement including demonstration of possession of the claimed invention is most justified.

As an example, in the \textit{Lilly} case, U.C. did not actually isolate and clone the human insulin cDNA until two years after filing the application listing the rat cDNA sequence.\textsuperscript{116} Clearly, the U.C. inventors were not in physical possession of the claimed invention to human sequences at the time of filing the patent application on the rat sequence, and a substantial amount of time and effort were still required to isolate, clone and sequence the human insulin cDNA.\textsuperscript{117} Thus, the \textit{Lilly} decision effectively prevented the U.C. inventors from overreaching and receiving patent protection for an invention which they did not possess at the time they filed their application.

However, once DNA is isolated and cloned from a natural biological source, it becomes an experimental molecule subject to human manipulation in the laboratory. For example, any cloned DNA

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\textsuperscript{115} Heller & Eisenberg, \textit{supra} note 110, at 699.
\textsuperscript{116} Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1562–63 (Fed. Cir. 1997).
\textsuperscript{117} See generally \textit{HALL}, \textit{supra} note 13 (describing the high-stakes race between three different research groups to clone the human insulin cDNA at issue in the \textit{Lilly} case).
\end{flushleft}
can be fragmented into smaller pieces and recombined with other DNA to create novel combinations. Moreover, any nucleotide sequence can be changed base-by-base at will to whatever the investigator desires it to be. It is in this context of nucleic acid sequences as experimental molecules that a broad interpretation of the written description requirement of the claimed invention is most justified as explained further below.

That is, if an inventor is limited to rights for a specifically listed DNA sequence, or to DNA sequences demonstrated to be in the inventor's possession, then it is a simple matter for a would-be infringer to create a variant of that DNA sequence that will encode the same protein (due to the degeneracy of the genetic code), or that will have substantially similar properties. Hundreds, even thousands of such variants could be created. Patent infringers could operate with impunity. Since it would be highly inefficient and impractical for an inventor to list all of the possible variant sequences covered by an invention merely to prevent infringement, this degree of specificity has never been required. Thus, broad claims that describe the DNA by characteristics other than sequence, such as by a structure-function relationship, will prevent patent infringers from avoiding liability by making minor changes to the claimed invention. Of course, other patent doctrines, such as novelty, nonobviousness and the doctrine of equivalents, may also come into play to prevent infringers from escaping liability.

The proposed primary cloning test addresses the dual nature of nucleic acids as both the subject of discovery and the subject of experimental manipulation and is as follows. First, primary cloning means the isolation and cloning of nucleic acids from a natural or primary biological source. Thus, for example, the cloning of human insulin cDNA from the mRNA of human pancreatic islet cells, the cells in the human body that produce insulin, is primary cloning, but the subsequent manipulation of that cloned cDNA is not. When analyzing the adequacy of the written description for a claimed

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118. See, e.g., ALBERTS, supra note 27, at 258–71.
121. The doctrine of equivalents refers to the judicially created doctrine by which courts extend the literal language of a claim to encompass additional subject matter that is so similar to that claimed that it is deemed equivalent. More specifically, this means that the infringing product or process "performs substantially the same function in substantially the same way to obtain the same result as the claimed subject matter." DONALD S. CHISUM, 5 CHISUM ON PATENTS § 18.04 (2002).
nucleic acid sequence, a court should consider whether the claimed sequence requires primary cloning, or whether it is a previously cloned molecule subject to experimental manipulation. When claims are to nucleic acids requiring primary cloning, then, in addition to providing a written description as outlined in the PTO Written Description Guidelines, the heightened requirement of physical possession of the claimed sequence must also be demonstrated. Requiring both an adequate written description and a demonstration of possession comports with a concept articulated by the Enzo II court: possession and written description are not synonymous. Satisfying both criteria for nucleic acids requiring primary cloning will provide "meaningful disclosure" of the invention and prevent overreaching by inventors who have not expended the effort, skill and creativity required to clone an original isolate from a biological source.

Adoption of the primary cloning test would also result in a requirement for actual reduction to practice. Although not required for the patentability of inventions in general, a requirement for actual reduction to practice in this narrow instance is reasonable in view of the fact that prior to the act of the primary cloning of a nucleic acid, the only form in which it exists is in nature. It is well established that natural phenomena are not patentable.

However, if the claimed nucleic acid sequence is an experimental molecule, other methods of describing the nucleic acid may be employed such that sufficient identifying characteristics are disclosed to distinguish the claimed sequence from others not claimed. Physical possession of all claimed sequences would not be required. This will allow inventors to protect the full scope of their inventions and prevent competitors from avoiding infringement by making minor changes to the claimed invention.

The primary cloning test thus incorporates the positive aspects of each side of the written description debate while effectively addressing the criticisms of each side. By focusing on whether the claimed nucleic acid requires primary cloning or not, courts can

122. Written Description Guidelines, 66 Fed. Reg. at 1110 n.42.
124. Id.
127. Id. (explaining that such characteristics include structure, binding affinity, binding specificity, molecular weight, length or combinations of characteristics).
adjust the written description and possession requirements accordingly. By requiring an adequate written description and a showing of possession for nucleic acids requiring primary cloning, courts will effectively narrow the scope of the claims. This will prevent overreaching by inventors, provide incentive and foster investment in research, and prevent a field from becoming monopolized by one or a few patent holders. However, by relaxing the written description requirement for experimental nucleic acids, courts will effectively broaden the scope of the claims. Then, the full scope of inventions is protected, investment in research is fostered and fields of investigation do not become overcrowded with narrow patents to overlapping inventions.

IV. APPLYING THE PRIMARY CLONING TEST TO THE ENZO '659 PATENT

The broadest claim of the Enzo '659 patent is to nucleotide sequences that bind preferentially to the genome of *N. gonorrhoeae* over the genome of *N. meningitides*, the preferential binding determined by following a series of steps beginning with radioactively labeling the said nucleotide sequence for use as a probe.\(^\text{128}\) Thus, the claim is to a nucleic acid probe. This is not a DNA molecule requiring primary cloning, but rather an experimental molecule. This is because to be used as a probe in this context, the DNA must have been previously cloned from a biological source.\(^\text{129}\)

Having determined that the claimed sequences are experimental molecules, the primary cloning test requires a broad construction of the written description requirement. The holding of the *Enzo II* court effectively takes this approach noting that DNA can be described by function if that function is correlated with a known or described structure.\(^\text{130}\) However, the CAFC left the factual determination of whether the functional DNA claim (here, hybridization) was sufficiently correlated with a known structure to the lower court.\(^\text{131}\)

How should the lower court approach this structure-function issue for the claimed nucleotide sequences? The CAFC noted that functional antibody claims are supported by an adequate written description because the structural characteristics and binding

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\(\text{128. '659 patent, supra note 11, claim 1.}\)

\(\text{129. See, e.g., ALBERTS, supra note 27, at 188–89.}\)

\(\text{130. Enzo Biochem, Inc. v. Gen-Probe, Inc., 296 F.3d 1316, 1324–26 (Fed. Cir. 2002).}\)

\(\text{131. Id. at 1327.}\)
functions of antibodies are so well known. The same can be said of the structural characteristics of nucleic acids and hybridization, characteristics that have been known to the scientific community and exploited experimentally for over 40 years. Thus, it would not be surprising if the lower court determined that the functional claim of hybridization was correlated with a sufficiently known structure thereby rendering the written description of Enzo’s hybridization claim adequate.

While such a finding in the case of the Enzo patent may be justified so that patent protection is awarded to cover the large number of variants that could be created experimentally simply to avoid patent infringement, what about other hybridization claims? What if, in the Lilly case, U.C. had claimed all vertebrate, mammalian and human cDNA sequences that hybridize to the rat insulin cDNA? Would insertion of just that one word, “hybridize,” into the claim render a specification with an inadequate written description suddenly adequate? Clearly, the answer must be “no,” otherwise this would represent a triumph of form over substance. It is for this reason that the primary cloning test proposed here requires a stricter showing of physical possession for claims to nucleic acids requiring primary cloning, such as those at issue in Lilly. Without a showing of physical possession, inventors “could receive patent rights to sequences of which they have no knowledge, in organisms with which they have never worked,” and perhaps never intend to work.

V. CONCLUSION

Throughout history, the written description requirement for patented inventions has been one of the most fundamental aspects of patents and reflects the quid pro quo nature of the patent system. In exchange for adequately describing the invention to one skilled in the art, the inventor receives a monopoly for a limited time during which others can be excluded from making, using or selling the invention.

Recent decisions of the CAFC indicate that the written description requirement plays an important role in determining the validity of claims to nucleic acid sequences, yet the court has not issued clear and consistent standards. In fact, the court itself appears confused over the proper standards by which to judge the adequacy of

132. Id. at 1324.
133. See, e.g., ALBERTS, supra note 27, at 188–96.
a written description as reflected by the recent decision in *Enzo I* followed by a reversal upon rehearing in *Enzo II*.

Thus, standards and guidelines are clearly needed to judge the adequacy of the written description supporting nucleic acid claims. One view is that the written description requirement should be broadly interpreted enabling inventors to maximize protection for their specific invention as well as related alternative embodiments. The opposing view is that the written description requirement should be narrowly interpreted thus preventing overreaching by inventors. Both sides claim that adopting their viewpoint will foster investment in research and result in the optimal number of patent holders in the industry.

In truth, both sides have merit and the opposing views can be reconciled by adopting the primary cloning test advocated here. The primary cloning test calls for distinguishing nucleic acid sequence claims between those molecules that have been isolated and cloned from a natural biological source and those that have not. Claims to molecules requiring primary cloning deserve heightened scrutiny as provided by the possession test first adopted by the *Fiers* court. In contrast, claims to previously cloned molecules, so-called experimental molecules, are supported by a broader application of the written description requirement and do not require a showing of physical possession. Thus, adoption of the primary cloning test will incorporate the best of both viewpoints resulting in broad protection for claims to nucleic acids that can easily be modified experimentally to avoid infringement and narrow protection for claims to novel nucleic acids that have not been previously isolated and cloned from a biological source.