

THE 2001 USPTO WRITTEN DESCRIPTION GUIDELINES AND GENE CLAIMS

By Eli A. Loots

The patent system attempts to “promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive rights to their respective writings and discoveries.”¹ In doing so, the patent system balances the goal of promoting research with the reward of offering exclusive protection of the invention. In order to ensure such a balance, a patent must meet certain requirements. The invention must be novel,² nonobvious,³ useful,⁴ of statutory subject matter,⁵ and enable one skilled in the art to make the invention.⁶ An additional requirement, embodied in section 112, is the written description of the invention.⁷ The scope of the written description requirement is unclear because of apparent inconsistencies in case law.

In order to help define the written description requirement, the United States Patent and Trademark Office (USPTO) issued the Written Description Guidelines (Guidelines) to explain how the requirement should be applied to incoming patent applications. It is not clear whether the Guidelines have resolved the inconsistencies in the field of biotechnology, perhaps because of inconsistencies in other areas of patent law. This is unfortunate because the written description requirement, in its current form, does not clearly promote research in the field of biotechnology.

© 2002 Berkeley Technology Law Journal & Berkeley Center for Law and Technology.

1. U.S. CONST. art. I, § 8, cl. 8.

2. 35 U.S.C. § 102 (1994).

3. 35 U.S.C. § 103 (1994).

4. 35 U.S.C. § 101 (1994).

5. *Id.*

6. 35 U.S.C. § 112 (1994).

7. “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.” *Id.*

I. BACKGROUND

A. Purpose of the Written Description Requirement

While the courts have articulated the written description requirement in slightly different ways, the factual inquiry is “whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed.”⁸

Such a description ensures that the patentee has possession over the claimed invention,⁹ so possession of the claimed invention will transfer to the public once the patent term has expired. In theory, the written description requirement ensures that the applicant actually invented the invention. Additionally, by forcing the inventor to describe what is claimed in the patent, we are able to ascertain if the inventor is trying to claim something that is already known.¹⁰ To this end, the written description can serve a notice function, both providing notice to the general populace that a new invention is being claimed and providing notice to future inventors of what has been claimed.¹¹ Finally, since the written description requirement is examined separately from other requirements (such as enablement), it ensures that what is actually claimed is clear. The requirement prevents expansion of the claimed subject matter through later amendment by requiring that any alterations be fully described in the original application.¹²

B. Purpose of the Guidelines

The Written Description Guidelines are intended to assist USPTO personnel in the determination of whether an adequate written description has been provided in a patent application.¹³ The Guidelines are derived from

8. U.S. Department of Commerce, Manual of Patent Examining Procedures § 2163.02 (7th ed., rev. Feb. 1, 2000) [hereinafter MPEP]. In theory, this is not a high standard to meet since, when reviewing a patent application, there is a strong presumption that an adequate written description is provided. *See In re Wertheim*, 541 F.2d 257, 263 (C.C.P.A. 1976).

9. 35 U.S.C. § 112; *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991).

10. *Evans v. Eaton*, 20 U.S. 356 (1822).

11. For a historical perspective of the evolution of the written description requirement, see Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 BERKELEY TECH. L.J. 615 (1998).

12. *See MPEP*, *supra* note 8, § 2163.

13. Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, ¶1 “Written Description” Requirement, 66 Fed. Reg. 1099, 1104 (Jan. 5, 2001) [hereinafter *The 2001 Written Description Guidelines*].

the USPTO's current understanding of the law and prior comments to the Interim Guidelines. Formally, the Guidelines lack any independent legal authority.¹⁴ The Guidelines state that a rejection of a patent application is based upon the substantive law itself, not the Guidelines.¹⁵ As such, inconsistencies within the Guidelines will result in inefficiencies, rather than a collapse of the patent system.¹⁶ Regardless, because of its central role in educating Patent Examiners, a thorough understanding of the Guidelines is helpful to patent attorneys in overcoming the hurdle of the written description requirement. Perhaps more importantly, any differences between the Guidelines and the current state of the law should be appreciated to ensure that an invention is adequately protected should the patent later face litigation.

C. Molecular Biology of DNA

While the new Guidelines are applicable to all inventions, they are particularly relevant in the area of biotechnology because several of the decisions that prompted the Guidelines involved inventions related to DNA.¹⁷

The desire to patent DNA sequences has dramatically increased in the last decade. This is due in part to new advances in technology, such as superior sequencing machines, sequencing techniques, and better computers (both for analysis and for sequencing). It is also due to a large influx of businesses into the biotechnology field, both from a biological and computational aspect. Finally, the increase in interest is due to the acknowledgment that new fields, such as genomics and proteomics, can cut years of research time from traditional scientific techniques thus, the information itself is valuable regardless of the particular function of a particular piece of DNA.¹⁸

14. *Id.*

15. *Id.* However, the USPTO states that, in light of the received comments to the Interim Guidelines, the present Guidelines are "believed to be fully consistent with binding precedent of the U.S. Supreme Court, as well as the U.S. Court of Appeals for the Federal Circuit and its predecessor courts." *Id.*

16. *Id.*

17. *See generally*, The 2001 Written Description Guidelines, *supra* note 13; Revised Interim Written Description Guidelines Training Materials, <http://www.uspto.gov/web/menu/written.pdf> (last visited Feb. 10, 2002) [hereinafter Interim Training Materials].

18. For instance, sequence comparison between various organisms relies on the concept of evolutionary conservation. As such, without knowing anything about a particular sequence, one is able to get an idea of a sequence's importance and even function, merely by its presence or absence across evolutionarily diverse species.

1. *General Composition of DNA*

A DNA sequence is a description of a series of nucleic acids or bases (adenine, cytosine, guanine, and thymine) covalently linked together.¹⁹ For the coding DNA to produce the protein it codes for, the DNA is first transcribed into a complementary strand of RNA.²⁰ This piece of RNA can then be translated into the protein for which it encodes.²¹ Enzymes read the sequence of nucleic acids in RNA as one might read a recipe in a cookbook, instructing the enzymes as to which amino acids need to be linked together to produce the desired protein.

2. *Properties of DNA that Make Patentability Difficult*

The largest problem with attempts to describe a DNA or protein sequence for a patent is that the sequences themselves are, on a base-by-base basis, relatively unimportant for the DNA or protein as a whole.²²

First, the genetic code itself is degenerate.²³ This presents the formal possibility that two people could each get a patent on the same amino acid sequence of a protein if it were described by different nucleic acid sequences. In practice, this is not an issue because, with relatively few exceptions, the genetic code is universal and well-known. That is, given any set of nucleic acids, one can predict the amino acid sequences that correlate to the nucleic acid sequence.²⁴

19. Some sections of the DNA molecule encode proteins. Such coding sections are termed exons; sections that do not code for proteins (noncoding) are termed introns. However, introns are not simply void of important biological information since elements within the introns regulate the expression of the coding exons. See BRUCE ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* 104-106 (3d ed. 1994).

20. *Id.*

21. *Id.*

22. This is exemplified by the practice of tryptophan and alanine scans, techniques for looking at key enzymatic sections of proteins, whereby each amino acid of a protein is progressively mutated and the properties of the protein examined for effects. The underlying assumption is that the vast majority of positions can be mutated without a substantial effect on the protein; only those unique sections of the protein which are biologically critical will alter the protein's properties. See, e.g., Li-Smerin, *A Localized Interaction Surface for Voltage-Sensing Domains on the Pore Domain of a K⁺ Channel*, 25 *NEURON* 411 (2000).

23. That is, each set of three nucleic acids (a triplet or codon) only encodes for a single amino acid; however, each amino acid may have different codons that encode for it. As such, two unique nucleic acid sequences may represent an identical amino acid sequence. ALBERTS ET AL., *supra* note 19, at 106.

24. In fact, given the right reading frame, one could predict the amino acid sequence with absolute certainty. Likewise, given the amino acid sequence, one could, with ease and absolute certainty, predict every possible combination of nucleic acid sequences that

Another problem is that the function of a protein (what it does and how it does it) is determined by the protein's structure. The protein's structure is determined by the amino acid sequence of the protein. Because of this relationship, in theory, one could predict the structure and function of a protein with nothing more than the sequence of the coding DNA.²⁵ In fact, the state of the art has now evolved to the point where rational protein design and modification, based on fundamental properties of the individual amino acids themselves, are now possible.²⁶ There are many types of interactions that occur along the amino acid chain which determine the protein's structure.²⁷ Surprisingly, the structure of a protein is predominately produced by a very large number of weak interactions. Because of this, the removal of any one of those small interactions will have practically no effect on the structure, and thus the function, of the protein.²⁸ A patent on a unique sequence, nucleic acid or amino acid, has no protective value since variations that do not alter the protein's function are common and easy to make.

3. *How Those In the Art View These Properties*

It has become a routine practice to identify and classify similar proteins in different organisms, as well as the functional parts of proteins, by comparing functionally equivalent sequences from different species

could encode the amino acid sequence. While the possible number probably would be very large, a standard table of the genetic code, found in most biology textbooks, would be all that was required. *See id.* at 106.

25. The “[s]hape of a [p]rotein [m]olecule is [d]etermined by its [a]mino [a]cid [s]equence”; “related structures often imply related functions”; and “the conformation of a newly sequenced protein domain can be guessed if it is homologous to a domain of a protein whose conformation . . . “ is known. *Id.* at 111, 123. *See also* Burkhard Rost, *Review: Protein Secondary Structure Prediction Continues to Rise*, 134 J. OF STRUCTURAL BIOLOGY 204 (2001) (stating that recent advances in protein prediction have resulted in a 76% accuracy rate in predicting the secondary state of amino acids in proteins).

26. *See, e.g.*, Scott A. Ross, *Designed Protein G Core Variants Fold to Native-like Structures: Sequence Selection by ORBIT Tolerates Variation in Backbone Specification*, 10 PROTEIN SCI. 450 (2001); Christopher A. Voigt et al., *Computational Method to Reduce the Search Space for Directed Protein Evolution*, 98 PROC. OF THE NAT'L ACAD. OF SCI. U.S.A. 3778 (2001); Shannon A. Marshall et al., *Achieving Stability and Conformational Specificity in Designed Proteins via Binary Patterning*, 305 J. OF MOLECULAR BIOLOGY 619 (2001).

27. Some of these interactions are very strong, such as disulfide bonds or charge interactions; others are very weak, such as van der waals interactions or hydrophobicity. ALBERTS ET AL., *supra* note 19, at 111-12.

28. *See* the previous discussion on this topic, *supra* note 22 (discussing the concept of the alanine and tryptophan scans).

(orthologs).²⁹ Sequences (either amino acid or nucleic acid) that are required for the protein to function are conserved between species. If such a critical element were changed, the protein would not function. If the protein were required for survival, the organism would be selected against evolutionarily. While critical elements are conserved between species, unimportant elements may vary.³⁰ Since this is all a function of time (or breeding cycles), organisms that evolved apart long ago show sequence similarities only at positions that are critical for function. Put another way, protein and nucleic acid sequences found in different species are the result of evolution over long periods. Thus, conservation of sequences between species allows identification of key structural elements in the sequences. Because of this, a critical sequence identified in a mouse is assumed to have a functionally and structurally equivalent sequence in humans and dogs. It is generally accepted that identification of the first member of any of these groups is not only the most difficult step in discovery, but also the most valuable since the sequence can be used to discover the equivalent sequence in another organism.³¹

29. ALBERTS ET AL., *supra* note 19 at 122 (stating that structural homologies can help assign functions to newly discovered proteins). See BLAST (presenting an actual tool for genomic comparisons), at <http://www.ncbi.nlm.nih.gov/BLAST> (revised Jan. 29, 2001); Systematics and Molecular Phylogenetics, at <http://www.ncbi.nlm.nih.gov/About/primer/phylo.html> (defining such a comparison and why such comparisons can be useful in other ways) (revised Nov. 31, 2001); and Molecular Modeling: A Method for Unraveling Protein Structure and Function, at <http://www.ncbi.nlm.nih.gov/About/primer/molecularmod.html> (revised Dec. 31, 2001) (describing one benefit of sequence comparison for structure determination). See also Tim Fergestad et al., *Targeted Mutations in the Syntaxin H3 Domain Specifically Disrupt SNARE Complex Function in Synaptic Transmission*, 21 THE J. OF NEUROSCIENCE 9142 (2001) (regarding an experiment based on amino acid conservation demonstrating key functional residues by conservation); Michael Wood et al., *Structural Conservation of Ion Conduction Pathways in K Channels and Glutamate Receptors*, 92 PROC. OF THE NAT'L ACAD. OF SCI. U.S.A. 4882 (1995) (using sequence homology to develop experiments and draw conclusions); Rosa Planells-Cases et al., *Mutation of Conserved Negatively Charged Residues in the S2 and S3 Transmembrane Segments of a Mammalian K⁺ Channel Selectively Modulates Channel Gating*, 92 PROC. OF THE NAT'L ACAD. OF SCI. U.S.A. 9422 (1995) (using sequence conservation to direct experimental efforts and draw conclusions).

30. See Martin Kreitman et al., *Coding Sequence Evolution*, 9 CURRENT OPINION IN GENETICS & DEVELOPMENT 637 (1999) (“[S]elective constraint on protein function must be the dominant mode of natural selection acting on amino acid replacement . . .”).

31. For instance, once one knows the sequence in one organism one may use segments of that sequence as a probe to find equivalent sequences in other organisms. Alternatively, if the genome is known, a simple BLAST search will reveal all similar sequences in minutes. A BLAST search can be performed by visiting the BLAST website. See BLAST, *supra* note 29.

D. Recent Legal Conflicts in the Written Description Requirement

Considering the mutability of DNA and amino acid sequences, sequences often need to be described in very broad terms to ensure adequate protection.³² Thus, many in the patent field have tried to describe DNA-based inventions in broad terms, without limiting the invention to the sole embodiment that was actually reduced to practice. Recent cases have addressed these attempts in conflicting manners.³³ A brief description of the cases is helpful in understanding the challenge that the USPTO faced in developing a unified definition of the written description requirement for the new Guidelines.

1. *Nonobviousness Cases*

While recent conflicts over the written description requirement have emphasized some internal inconsistencies, the source of these problems may have originated in case law concerned with issues of nonobviousness.

a) *In re Deuel*

While the issue in *In re Deuel*³⁴ was one of “obviousness,” the holding has had a profound effect on the issue of adequate written description. Deuel’s invention involved a process for isolating and purifying specific DNA molecules, in the context of a method for gene cloning and a partial amino acid sequence of the protein.³⁵ Deuel challenged the Board of Patent Appeals and Interferences’ finding of obviousness of his invention. The court held that disclosure of a particular protein’s sequence does not necessarily render a DNA sequence encoding that protein obvious because of the redundancy in the genetic code.³⁶ Effectively, the court minimized the analytic role of “one skilled in the art” and simply required the USPTO and courts to hold DNA sequences to be nonobvious over amino acid sequences. Interestingly, the USPTO has refused to follow this in the current

32. This is especially true since minor variations are easy to produce once the initial work is done, e.g. a single point mutation via a “Quickchange mutagenesis kit,” a kit mass-produced by Stratagene.

33. See generally Limin Zheng, Note, *Purdue Pharma L.P. v. Faulding Inc.*, 17 BERKELEY TECH. L.J. 95 (2002) (describing recent cases involving the written description requirement for biotechnology patents).

34. *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).

35. *Id.* at 1554-1557.

36. “[A] prior art disclosure of the amino acid sequence of a protein does not necessarily render particular DNA molecules encoding the protein obvious because the redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein.” *Id.* at 1558.

Written Description Guidelines, instead favoring what one skilled in the art would realize from an amino acid sequence.³⁷

b) *In re Bell*

Similar to *Deuel*, Bell challenged the USPTO's finding that his inventions, the nucleic acids of the Preproinsulin-Like Growth Factors I and II, were obvious in light of a prior amino acid sequence of the protein and an enabling method to isolate it.³⁸ The court rejected the idea that such a nucleic acid sequence was obvious, primarily because of the vast number of possible nucleic acid sequences that could correspond to the specified amino acid sequence.³⁹ Bell specifically claimed *human* insulin. As such, the "unique" DNA sequence for human preproinsulin was not obvious out of the large number of possibilities described by the amino acid sequence.⁴⁰ The USPTO has used the court's holding in *Bell* as a means for limiting the USPTO's departure from the rules suggested in *Deuel*. While one can describe a nucleic acid by describing an amino acid, the USPTO has refused to grant each possible species in such a genus to an inventor, though the genus itself is described.⁴¹

2. *Written Description Cases*

a) *Vas-Cath v. Mahurkar*

Mahurkar relied on drawings of his double lumen catheter in one of his previous patents as support for a range of lumen ratios for a new utility patent.⁴² While the original patent only contained a single ratio, the Federal Circuit held that the drawings were sufficient for an adequate written description of a range of ratios.⁴³ The court held that the written description is not limited to what is literally described; rather, it includes what one skilled in the art would be aware of as limitations.⁴⁴ This opinion has served as an expansive interpretation of the written description require-

37. The 2001 Written Description Guidelines, *supra* note 13, at 1102 ("[T]he question of possession of a class of nucleotides encoding that polypeptide can be addressed as a relatively routine matter using the understanding of the genetic code . . .").

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

39. *Id.* at 784.

40. *Id.*

41. "[T]his does not mean that applicant was in possession of any particular species of the broad genus" and "possession of a large genus did not put a person of ordinary skill in the art in possession of any particular species." The 2001 Written Description Guidelines, *supra* note 13, at 1102.

42. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1558 (Fed. Cir. 1991).

43. *Id.* at 1566.

44. *Id.*

ment, allowing one to incorporate the knowledge of one skilled in the art in fulfilling the written description requirement.

b) *Amgen, Inc. v. Chugai Pharmaceutical, Co.*

Amgen alleged that Genetics Institute and Chugai Pharmaceutical's patents infringed Amgen's patent on the DNA sequence of human erythropoietin (EPO).⁴⁵ Genetics Institute possessed a prior patent on purified human EPO that also included in the specification a disclosure (although not an enabling disclosure)⁴⁶ for obtaining and using the DNA sequence of human EPO.⁴⁷ The court suggested that an inventor might need actual reduction to practice to establish inventions such as DNA sequences.⁴⁸ The court required this because an inventor would not be able to distinguish one sequence from another without actually knowing both sequences.⁴⁹ Thus, the court found that Genetics Institute's description was not a sufficient written description of the DNA sequence.⁵⁰ Some have read *Chugai* as the first in a series of decisions tending toward a per se rule for sequence patents rather than from the perspective of one skilled in the art.⁵¹ However, the court in *Chugai* declined to hold that a per se rule was required, stating that there might be other "characteristics sufficient to distinguish [a gene] from other genes."⁵²

c) *Fiers v. Revel*

Unlike *Amgen*, where the description was not enabling, *Fiers* had actually described a method that enabled one skilled in the art to isolate the protein of interest (beta-interferon).⁵³ In an attempt to distinguish *Amgen*, *Fiers* asserted that *Amgen* only applies to nonenabling disclosures, and that an enabled disclosure for a method of isolation is sufficient to describe an invention.⁵⁴ The court disagreed with *Fiers*' assertion and stated that allowing such a policy would allow would-be inventors to obtain patents before they had invented anything.⁵⁵ Such a policy would promote the dis-

45. *Amgen, Inc. v. Chugai Pharmaceutical, Co.*, 927 F.2d 1200, 1203 (Fed. Cir. 1991).

46. *Id.* at 1207.

47. *Id.* at 1204-6.

48. *Id.* at 1206.

49. *Id.*

50. *Id.*

51. *See* Mueller, *supra* note 11, at 631, n.92 (1998).

52. *Id.* at 1206.

53. *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993).

54. *Id.* at 1169.

55. *Id.*

closure of research plans, rather than inventions.⁵⁶ Additionally, a second patent applicant, Revel, attempted to claim the DNA sequence by stating that it was part of the invention and including a reference for obtaining the DNA.⁵⁷ However, the court reemphasized its initial rejection of Fiers' application, stating that the inventor was required to produce a description of the DNA itself.⁵⁸

The third applicant, Sugano, did have an adequate written description of the DNA. Sugano's application disclosed the entire sequence of beta-interferon in addition to containing an enabling disclosure of how to obtain the sequence.⁵⁹ The court seemed to be requiring an actual reduction to practice even where the inventor had provided enabling disclosures.

d) *Regents of the University of California v. Eli Lilly & Co.*

In 1977, the University of California (U.C.) discovered and patented the cDNA of insulin using the DNA sequence of rat insulin.⁶⁰ The patent also claimed "mammalian" and "vertebrate" insulin, and it provided enabling methods for obtaining such sequences.⁶¹ The patent did not provide sequences themselves.⁶² The University of California then filed suit against Eli Lilly for its production of human insulin.⁶³ Relying on *Fiers*, the court stated that enabling an invention is not synonymous with an adequate written description.⁶⁴ The court suggested that possession is not demonstrated without the complete sequence of the cDNA, since one skilled in the art would not recognize the invention without such an actual reduction to practice of the DNA sequence.⁶⁵

While the amino acid sequence of human insulin was disclosed in the U.C. patent, the court used *Deuel* to state that a DNA sequence is, by definition, nonobvious in light of an amino acid sequence. The court went even further, however, stating that even if a description makes an invention obvious, it may not suffice for the written description requirement.⁶⁶ As such, it appears that even if something is obvious and enabled, one

56. *Id.*

57. *Id.* at 1170.

58. *Id.*

59. *Id.* at 1172.

60. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).

61. *Id.* at 1563.

62. *Id.* at 1562-3.

63. *Id.* at 1562.

64. *Id.* at 1567.

65. *Id.* at 1568.

66. *Id.* at 1567.

may not have actually described it. The court found such a situation acceptable since the “level of skill in the art” was very low.⁶⁷

Generally, the USPTO has interpreted *Lilly* to mean that a description by function is not sufficient for a DNA claim.⁶⁸ In order to avoid any appearance of conflict between *Vas-Cath* and *Lilly*, the USPTO has stated that *Lilly* “explains that a chemical compound’s name does not necessarily convey a written description . . . particularly when a genus of compounds is claimed.”⁶⁹ In effect, one skilled in the art cannot “visualize or recognize the identity of the members of the genus.”⁷⁰ Presumably this is so because of the “unpredictability” or low “level of skill in the art,” a factor the court and the USPTO seem to have interpreted as determinative of all other facts in the written description requirement.

II. THE GUIDELINES

The new Guidelines outline a three-step process for analyzing a written description. First, one must determine what the claim covers as a whole.⁷¹ Second, one must examine the application to determine *how* support is provided for the claimed invention.⁷² Finally, one determines whether the written description is sufficient to inform one skilled in the art that the applicant possessed the invention as a whole at the time the application was filed.⁷³ Possession can be demonstrated by: (a) reduction to practice;⁷⁴ (b) a clear depiction;⁷⁵ or (c) a disclosure of relevant, distin-

67. *Id.* at 1568.

68. The 2001 Written Description Guidelines, *supra* note 13, at 1110, n.43.

69. *Id.* at 1100.

70. *Id.* (quoting *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997)).

71. *Id.* at 1105. Additionally, each claim must be given its broadest reasonable interpretation in view of the written description. *Id.*

72. *Id.* This includes an examination of the specific embodiments, figures, and sequence (nucleotide or amino acid) listings. It is at this point that one must determine which field and what level of skill is present in the art of the invention. The Guidelines note that information that is well known in the art need not be described in detail. *Id.* Accordingly, there is a lower requirement for a description in technologies with a high level of skill in the art, while there is a higher requirement for technologies that have a lower amount of knowledge and skill. *Id.*

73. *Id.* at 1105-6.

74. *Id.* at 1105.

75. *Id.* A clear depiction can be achieved by detailed drawings and structural formula. *Id.*

guishing, and identifying characteristics.⁷⁶ At this point, one considers whether there is sufficient evidence of possession.⁷⁷

The USPTO specifically indicates that in technologies that are mature, the written description requirement is met, even if the description only discloses a method of manufacturing the invention and the function of the invention.⁷⁸ For young or unpredictable technologies, however, more evidence is required to show possession.⁷⁹ This heightened standard also applies if the invention is characterized by factors which are not reasonably predictable. In order to determine the maturity of the art or the level of skill in the art, the USPTO uses patents and printed publications.⁸⁰

The USPTO also describes the requirements for obtaining a claim on a genus, a core claim for many DNA claims. In addition to the previous three requirements, the claim must describe a "representative number of species."⁸¹ A claim describes a representative number of species when the described species "are representative of the entire genus."⁸² For instance, in a genus that encompasses widely variant species, disclosure of a single species is insufficient.⁸³ However, the level of description for the species does not have to be so great as to provide support for each species individually.⁸⁴

76. *Id.* Identifying characteristics include, physical/chemical properties, functional characteristics combined with a structure/function correlation, and complete or partial structures (either amino acid or nucleic acid). *Id.* at 1106.

77. In situations where a complete structure is disclosed, the written description requirement is satisfied. If a complete structure is not disclosed one considers such factors as, level of skill in the art, partial structures, physical/chemical properties, functional characteristics, functional characteristics with additional structure/function correlations, and the method for making the invention. "Disclosure . . . of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is . . ." the requirement that the above factors must demonstrate. *Id.* For a full description of such scenarios, see *Id.*

78. *Id.* at 1106 (citing *In re Hayes Microcomputer Products, Inc.*, 982 F.2d 1527, 1534-35 (Fed. Cir. 1992)).

79. *Id.*

80. *Id.*

81. *Id.*

82. *Id.* Additionally, the USPTO specifically notes that there may be situations where a single species represents an entire genus. *Id.* at 1110, n.55. However, the USPTO specifically prohibits this for DNA descriptions. *Id.* at 1111, n.56.

83. *Id.* at 1106.

84. *Id.* at 1106. "For example, in the molecular biology arts, if an application disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence." See *Id.* at 1111 n.57.

III. DISCUSSION

A. Inconsistencies between the Guidelines and Prior Case Law

Since the prior case law upon which the Guidelines are based may be inconsistent,⁸⁵ it is not surprising that the new Guidelines can be interpreted as conflicting with prior case law. This is most noticeable in the area of biotechnology involving DNA sequences. While the court in *Lilly* held that claiming a nucleic acid sequence by describing an amino acid sequence was not an adequate description of the invention,⁸⁶ the Guidelines suggest otherwise.⁸⁷ Additionally, while the court in *Lilly* held that stating the name of a DNA sequence is not an adequate description,⁸⁸ the Guidelines allow descriptions of sequences in terms of percent identity,⁸⁹ a description arguably equivalent to stating a name.⁹⁰ This differs from the prior case law not only by allowing a functional term to define the sequence, but also because the use of percent identity results in potentially huge numbers of sequences that are described by the patent.⁹¹ Such a deviation starts to erode the per se rule of nonobviousness that cases such as *Bell*⁹² and *Deuel*⁹³ have suggested.

One manner in which the USPTO can attempt to justify these differences is that the “level of knowledge in the art” of biotechnology when the patent in *Lilly* was issued was low, and thus the patent required more description than is required of a biotechnological invention of today.⁹⁴ This

85. See discussion, *supra* Part I.D.

86. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1567 (Fed. Cir. 1997).

87. The 2001 Written Description Guidelines, *supra* note 13, at 1102 (stating that nucleic acid sequences can be determined from amino acid sequences).

88. *Lilly*, 119 F.3d. at 1567 (“[T]he name cDNA is not itself a written description of that DNA. .”).

89. “[T]here is no basis for a per se rule . . . limiting DNA claims to only the sequence disclosed.” The 2001 Written Description Guidelines, *supra* note 13; *see also*, Interim Training Materials, Ex. 14, *supra* note 17, at 53-55.

90. For instance, one might consider the statements 1) sequence X is 80% identical to proteins that are of group Y, and 2) a sequence belonging to the group Y (which consists of proteins that are 80% identical), to be equivalent.

91. For instance, there are 5^{20} permutations of a 100 amino acid sequence with 95% identity.

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

93. *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).

94. Some suggest “that, with regard to biotechnological inventions, as the general knowledge and skill in this art improves, the PTO will allow increasingly broader claims. . . . This position reflects the argument that while the state of DNA inventions was once unpredictable, today the state of the art has advanced to the point where isolating nucleotide sequences is routine to persons skilled in the art, and therefore predict-

concept is in keeping with part of the *Lilly* decision and is reiterated in the Guidelines as the factor of the “level of skill and knowledge in the art.”⁹⁵ However, many believe that the “level of skill in the art” at the time of the filing of the *Lilly* application was sufficiently high that “one of skill in the art” would have understood what U.C. meant by its description of mammalian insulin in its original patent.⁹⁶ While debatable, the USPTO suggests that regardless of the changes that may have occurred in the art of biotechnology over the last two decades, such changes are not sufficient to render the claims in *Lilly* as adequately described, even at today’s “level of skill in the art” of biotechnology.⁹⁷

Many have seen *Lilly* as a departure from the fact-based standard of what one skilled in the art would recognize, to a legal rule that some written descriptions are per se inadequate.⁹⁸ Concerning biotechnology, many have viewed *Lilly* as requiring the recitation of the literal nucleic acid sequence for an adequate written description. Because of this requirement, commentators have suggested that *Lilly* “reflect[s] an increasingly-widening gulf between the norms of the business and scientific community and those of the United States patent system.”⁹⁹ Given this interpretation of *Lilly*, the USPTO’s allowance of claims using amino acids and percent homology are in conflict with the court’s requirement, as in *Lilly*, that the application recite a sequence.¹⁰⁰

able.” Margaret Sampson, *The Evolution of the Enablement and Written Description Requirements Under 35 U.S.C. 112 in the Area of Biotechnology*, 15 BERKELEY TECH. L.J. 1233, 1267 (2000).

95. The 2001 Written Description Guidelines, *supra* note 13, at 1106.

96. “Persons skilled in the art of recombinant DNA technology were very likely to have understood that by making the rat insulin cDNA, the UC inventors conceptually possessed the human insulin cDNA (if not all mammalian cDNAs).” Mueller, *supra* note 11, at 652 (1998). For instance, the genetic code which allows one to predict (in a functional manner) nucleic acids from amino acids was known long before the U.C. patent was written in 1979. See Marshall Nirenberg & Christian Wunsch, *RNA Codewords and Protein Synthesis*, 145 SCIENCE 1399 (1964). In addition, homology is a concept that has been ingrained in biology from the first days of taxonomy and was acknowledged specifically on the protein level before the *Lilly* decision as well. See Marshall Needleman & Philip Leder, *A General Method Applicable to the Search for Similarities in the Amino Acid Sequence of Two Proteins*, 48 J. MOL. BIOL. 443 (1970).

97. Interim Training Materials, Ex. 17, *see supra* note 17, 61-64.

98. “The *Lilly* court’s per se rule that a claim to a cDNA must be described in terms of its specific nucleotide sequence fails to address fact-specific questions concerning the state of the art and the level of skill among art workers, from whose perspective the written description inquiry must be answered.” Mueller, *supra* note 11, at 651.

99. *Id.* at 652.

100. This is emphasized by the USPTO’s statement that there is no per se rule concerning the requirements for patenting a DNA sequence. The 2001 Written Description

B. Inconsistencies within the Guidelines

Despite the progressive nature of some of the requirements, the Guidelines are not as broadening as one might first suspect. For instance, while the Guidelines depart from prior case law in a fairly permissive manner,¹⁰¹ the comments in the Guidelines also state that a genus claimed by name is not sufficient because one cannot identify the members of the genus.¹⁰² Additionally, descriptions consisting only of the function of the invention are insufficient to achieve an adequate written description if they only indicate what the composition does, rather than what it is.¹⁰³ Finally, the factor of the “level of skill in the art” limits any relaxation of the written description requirement. In effect, the ability to ignore what one skilled in the art may know, because the Examiner has declared that some element in the field is too uncertain,¹⁰⁴ allows the Examiner to require actual reduction to practice.¹⁰⁵

The implementation of the rules in the training examples makes the inconsistencies clear. For instance, according to the USPTO, if a scenario similar to *Lilly* occurred today, the USPTO would reject the application for failing to satisfy the written description requirement.¹⁰⁶ A comparison of the Examples in the training materials, in particular the *Lilly* Hypothetical in Example 17 and the more progressive Examples, may be helpful in describing these inconsistencies.¹⁰⁷

Guidelines, *supra* note 13, at 1101. Even more impressive is the USPTO’s statement regarding the requirements to claim a genus of DNA sequences by describing an amino acid sequence. The 2001 Written Description Guidelines, *supra* note 13, at 1101-1102.

101. There is no “per se rule requiring disclosures of complete DNA sequences or limiting DNA claims to only the sequences disclosed.” *Id.* at 1101. Amino acid sequences appear to be sufficient for claiming the equivalent nucleic acid sequence. *Id.* at 1102. There is even an admission that a single species would be sufficient to claim a genus “when the description of the species would evidence to one of ordinary skill in the art that the invention includes the genus.” *Id.*

102. Although a search of the National Center for Biotechnology Information’s database by a single protein’s name would yield a genus of sequences with regions of conservation. Presumably, the regions of conservation would automatically identify the critical structural elements of the protein that one skilled in the art would recognize as critical for that particular protein.

103. The 2001 Written Description Guidelines, *supra* note 13, at 1101.

104. Uncertainty can arise either in the art itself or in the features that define the claim.

105. The 2001 Written Description Guidelines, *supra* note 13, at 1101.

106. This is also the strongest evidence that the differences between the Guidelines and *Lilly* cannot be attributed to a change in the level of skill in the art since the USPTO is still claiming that such a claim would not be sufficient.

107. Interim Training Materials, *supra* note 17, at 61-64.

C. Example 17 Demonstrates the Guideline's Inconsistencies

Example 17 of the training materials presents a fact scenario identical to *Lilly*. As in *Lilly*, the patent recites a sequence for rat cDNA of proinsulin,¹⁰⁸ as well as a method for determining other cDNA sequences.¹⁰⁹ In analyzing the adequacy of the description, the Example discusses four factors: 1) the absence of human insulin cDNA; 2) variability of insulin cDNA; 3) the absence of evidence concerning how the structure of rat cDNA could provide structural evidence of human cDNA, based on rat cDNA; and 4) the absence of evidence that the rat cDNA had a known structural relationship to the human cDNA. The Example then concludes that the written description requirement is not met.¹¹⁰ This decision concurs with the holding in *Lilly*.¹¹¹ However, it is unclear how this result is justified when each of the four factors is satisfied under the new Written Description Guidelines.

1. *No species of human insulin cDNA is disclosed*

While no human cDNA is literally defined in Example 17, one skilled in the art could equate the given human amino acid sequence with the genus of nucleic acid sequences claimed.¹¹² The Guidelines explicitly recognize this.¹¹³ Additionally, by sequence comparison of the given rat and human sequences, it is possible to obtain an idea of the percent identity (and thus sequence) of even the missing elements that encode the "pre" aspect of the pre-proinsulin.¹¹⁴ Finally, the Guidelines suggest that an

108. Proinsulin is a biological precursor of insulin. The example also includes pre-proinsulin, a precursor of proinsulin.

109. Interim Training Materials, *supra* note 17 at 61-64. Additionally, the example stipulates that the amino acid sequence of human proinsulin is known. However, it is stated that the human insulin sequence may vary, and that insulin is post translationally modified. There is a genus claim directed to isolated human cDNAs which encode insulin. *Id.*

110. *Id.* at 64.

111. Interestingly, while the facts and outcome are identical, the "level of skill in the art" is not since the field has had 20 years to develop since the U.C. patent in *Lilly*. As such, the theory that the result in *Lilly* would not occur today, because there is a higher level of skill in the art, is not consistent with the USPTO's Interim Training Materials.

112. See previous discussion on this topic, *supra* note 24.

113. The 2001 Written Description Guidelines, *supra* note 13, at 1102 ("[P]ossession of a class of nucleotides encoding that [amino acid sequence] can be addressed as a relatively routine matter . . .").

114. For instance, a quick comparison of the amino acid sequences of the rat and human insulin protein by BLAST may yield a percent identity of 84% (88% similarity). *Supra* note 29. In theory, assuming that the functional aspects of the protein should be conserved and that the pre and pro elements of insulin are functional, one should also

amino acid sequence would suffice for a genus claim of the nucleic acids.¹¹⁵

2. *Variation among individuals*

Variability of proteins across individuals should be allowed in the written description requirement. The USPTO rejects the idea that sequences can only be claimed by a literal recitation of the sequence.¹¹⁶ All that is required is that the species be representative of the structures of the entire genus.¹¹⁷ As noted by Example 9¹¹⁸ and Example 14,¹¹⁹ there are multiple methods for demonstrating genus claims with a *single* species, even if it is a piece of DNA. The important element is that the structurally functional features of the genus (the common element in each species) are described to one of skill in the art, keeping in mind that unimportant elements need not be described.¹²⁰ Such a description is present here (constructively) because the amino acid sequences of rat and human insulin allow one to predict the critical structural elements of the protein, and thus of the cDNA for insulin.¹²¹ Additionally, variation among individuals is not a relevant concern because such variations, presumably, do not alter the underlying invention.¹²²

3. *Lack of a structure/function relationship*

The remaining factors, the lack of a structure/function relationship between the rat and human cDNA, simply ignore the knowledge of one

have an idea of the percent homology of the pre and pro regions of the human cDNA (84/88%) from the rat sequence.

115. 2001 Written Description Guidelines, *supra* note 13, at 1102.

116. *Id.* at 1101.

117. *Id.* at 1106.

118. *Interim Training Materials*, *supra* note 97, at 35-37 (demonstrating a description of a genus with a single species by using stringent hybridization conditions).

119. *Id.* at 53-55 (using percent identity to describe a genus with a single species).

120. 2001 Written Description Guidelines, *supra* note 13, at 1106.

121. Additionally, since a BLAST search results in a rat to human comparison of 84%, the phrase, "human insulin cDNA" includes the DNA sequence that has "84% identity to rat cDNA." See BLAST, *supra* note 29. Because of this functional equivalence, it could be argued that there should be no difference between the use of an agreed upon name or scientifically agreed upon percentage.

122. For example, assuming insulin functions the same in each human, or even in mammals, variations in the cDNAs between the organisms are not necessary for the operation of the protein. Since these variations aren't part of the invention, the variations may be defined as irrelevant features of the invention. Since irrelevant features of an invention never need to be disclosed, these variations need not be described in the written description.

skilled in the art. The simplest comparison¹²³ between amino acid sequences of the two organisms will demonstrate conserved areas in the sequences. Presumably these areas are conserved because they are required for protein function. Conservation thus defines the structurally significant areas of the nucleic acid sequences of both the rat and human cDNA.¹²⁴ As such, the critical structural relationships between the human and rat amino acid sequence, and constructively the nucleic acid sequence, would be routine for one skilled in the art to determine, and thus need not be disclosed. The assertion that there may be substantial variation among the species is meaningless. It is evident that the key structures for the desired functions are conserved between species since insulin protein function is conserved across a wide range of organisms.¹²⁵ Since the sequences that make the protein function are conserved, the unique sequences of the possible variations of insulin do not need to be described because these highly variable sequences are not elements that are essential to the invention.

Thus, it appears that the knowledge of one skilled in the art has been deemed lacking in this scenario. Presumably, this is for the same reason that the court in *Lilly* found, that the "level of skill and knowledge in the art" was too low to allow such a claim.

D. Per se Rules are the Source of the Inconsistencies

Some conflict between patent prosecution and patent litigation is inevitable. However, the current conflict has been recognized as a widening gulf between the norms of the scientific community and those of the legal system.¹²⁶ As such, the USPTO and the courts seem willing to treat the written description requirement as a legal issue,¹²⁷ as opposed to a

123. For instance, the use of a program such as BLAST is a common method of analyzing sequences. See BLAST, *supra* note 29.

124. See, e.g., J. Michael Conlon, *Evolution of the Insulin Molecule: Insights into Structure-Activity and Phylogenetic Relationships*, 22 PEPTIDES 1183 (2001) (applying such a comparison for fifty sequences of insulin).

125. Additionally, for an item such as insulin where there is a long history of cross species equivalence of the protein between various organisms, one skilled in the art would take the structural similarities between the insulin proteins of various organisms to be highly conserved, without additional evidence. See ALBERTS ET AL., *supra* note 19, at 122.

126. "Since the addition of *Lilly* to the *Fiers v. Revel* decision, scholars and commentators alike have argued that the rulings are a radical departure from traditional description requirement jurisprudence." Lisa A. Karczewski, *Biotechnological Gene Patent Applications: The Implications of the USPTO Written Description Requirement Guidelines on the Biotechnology Industry*, 31 MCGEORGE L. REV. 1043, 1064-5 (2000). One reason for such a gulf may be due to the fact that the requirements for something to be "obvious" in a legal sense do not accurately reflect what is scientifically "obvious." See MUELLER, *supra* note 11, at 615 (1998).

written description requirement as a legal issue,¹²⁷ as opposed to a question of fact.

In the particular instance of DNA technology, it seems that the origin of the current problems may be traced back to courts' decisions in *In re Bell*¹²⁸ and *In re Deuel*.¹²⁹ While these decisions may have been technically correct as far as the nonobviousness analysis were concerned, these holdings promote patenting previously discovered sequences by simply altering a single amino or nucleic acid. While greatly limiting the protection that many of the DNA inventions received,¹³⁰ the holdings of *Bell* and *Deuel* had a larger negative impact—the development of per se rules.

E. Per se Rules and the “Level of Skill in the Art” are Self-Defeating for Promoting Certain Research in Biotechnology

A system that ignores the ability of one skilled in the art by using per se rules may actually inhibit downstream product optimization research while also removing the incentive for upstream, basic research.¹³¹ This is particularly relevant in biotechnology. The combination of the reduction of informational barriers, an emphasis on granting patent protection only to optimized products, and the certainties of FDA testing costs, result in a scenario where downstream research is the only area encouraged. However, there is little protection for getting to, or finding value in, the final product.

1. Informational barriers protecting drug optimization are disappearing

A patent is traditionally a reward for a completed invention, not a license to hunt for one.¹³² While this may have been the proper role of a patent in biotechnology in the past, it is not clear that an overly strict application of this idea is appropriate now. The amount of information that is available to the skilled artisan has dramatically increased in the biotech-

127. For example, the development of per se rules concerning the obviousness of DNA sequences or the USPTO's deferring to the court's holding in *Lilly* in Example 17 of the Interim Training Materials. Interim Training Materials, *supra* note 17, at 61-64.

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

129. *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).

130. Often to a point of uselessness, as for example, limiting the invention to rat insulin as in *Lilly*. See *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997).

131. Whether this information is ignored simply for per se rules or because the USPTO has declared that the “level of skill in the art” is low, may not matter because the key factor for this analysis is that “one skilled in the art” is able to avoid another's patent without an inventive step.

132. *Brenner v. Manson*, 383 U.S. 519, 536 (1966).

nology field, primarily because of progress in the sequencing of entire genomes. Requiring a reduction to practice because of a low "level of skill in the art," as in *Lilly*, also increases the amount of information available to the practitioner.¹³³ The availability of this information reduces the initial barrier for entering the field of drug design, as well as the amount of protection that trade secrets can provide late in that area. The result may be that the financial risk in drug development has now been shifted from discovery to optimization of a target drug.¹³⁴ Such a shift is consistent with the general goals of the court in *Lilly* because only disclosure of the *final species* is sufficient. It is not clear that drug design will actually be encouraged by this shift.

2. *Per se rules discourage pioneering work but favor optimization*

The patent system has traditionally granted broad protection to pioneers in a field.¹³⁵ The courts and the USPTO have changed this by granting less protection to pioneers in uncertain fields (i.e., fields with a "low level of skill in the art"). This is a disincentive for pioneering work, but may be an incentive for optimizing existing inventions.¹³⁶ This is particularly true with regard to the current written description requirement, because inventions may be obvious and enabled, but may still escape protection.¹³⁷

133. For instance, patents could fully enable but not protect obvious targets for downstream inventions. *See Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997) (holding that enablement of an invention does not provide an adequate description of the invention and that a description which renders something obvious may not provide an adequate written description).

134. Interestingly, this early part of the process usually involves shifting from animal to human models, a process obviously not encouraged by the court's decision in *Lilly*. *See id.* (holding that a description which is adequate for rat insulin is not adequate for human insulin).

135. *See generally* *Boyden Power Brake Co. v. Westinghouse*, 170 U.S. 537, 569 (1898). *See also* 5A DONALD S. CHISUM, CHISUM ON PATENTS §18.02[2] (1998).

136. For instance, people may choose optimization because: a) it is relatively easy compared to pioneering work, and b) it is the only area in which they can get patent protection.

137. For instance, following the court's decision in *Lilly*, there is no longer an incentive for the U.C. to disclose the sequence of a rat protein and a method for obtaining the same sequence from humans, because another entity, with more resources, can use the disclosed information to obtain the literal sequence first.

3. *Drug optimization is discouraged without adequate upstream protection*

While optimization may be an appropriate goal of the patent system, promotion of research at this point in the research stream may not be adequate to encourage downstream research, such as optimization of drug technologies, in biotechnology. If initial patent protection is too narrow and competitors can readily identify and create alternative, but equivalent, embodiments of the invention, it is safe to assume they will.¹³⁸ While this may initially attract researchers to the point in the research stream where drug candidates are being selected (since a “new” invention can be easily obtained),¹³⁹ this is a disincentive in the development of further downstream research or optimization of the drug. The existence of numerous alternative but equivalent drug candidates is a guarantee that the value of the drug will be much less when it enters the market, because the drug will hit the market at approximately the same time as its equivalents.¹⁴⁰

Adequate protection for biotechnology inventions may be required further upstream than adequate protection for many other fields because of the huge and relatively certain costs of FDA approval and the ease of making equivalent variants that are, per se, nonobvious.

IV. CONCLUSION

The individual differences between prior case law and the Guidelines, as well as inconsistencies within the Guidelines themselves, may be due to the USPTO’s attempt to combine both per se rules and factors such as “the level of skill in the art” with the actual knowledge and ability of one skilled in the art. To the extent that the Guidelines encourage the analysis of the written description requirement as an issue of fact, the purposes behind the patent system will be well served.

138. This may be exacerbated if the patent system itself is encouraging improvement patents over pioneering patents, guaranteeing that inventions with minor modifications will be given as much protection as any other invention.

139. For example, by introducing a point mutation or finding the gene’s ortholog in another organism, “novel” but functionally identical inventions may be readily “discovered.”

140. In effect, allowing generics to enter the market when the original enters.

