THE 2001 PTO UTILITY EXAMINATION GUIDELINES AND DNA PATENTS

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Over the last half century, biotechnology has made tremendous contributions to medicine, agriculture, and industry. The understanding of basic biochemical processes has led to innovative methods of diagnosing and treating disease.[1] Modern agricultural advances have facilitated the introduction of essential nutrients into staple crops in under-developed countries.[2] With the pace of innovation showing no sign of slowing, the biotechnology industry holds even greater promise in the coming century.[3]

Many biotechnology research efforts focus on recombinant methods of copying, manipulating, and controlling deoxyribonucleic acid ("DNA").[4] In the past decade, both government and private efforts have succeeded in sequencing the genomes[5] of entire organisms, including humans.[6] DNA sequencing efforts have resulted in an enormous number of patent applications directed to DNA compositions.[7]

The initial responsibility for determining the patentability of inventions rests with the U.S. Patent and Trademark Office ("PTO"), which examines patent applications for compliance with statutory requirements. In response to concerns that the PTO granted proprietary rights to biotech-

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1. *See* BRUCE ALBERTS, ET AL., MOLECULAR BIOLOGY OF THE CELL 291 (3d ed. 1994).

2. *See* Dennis Normile, *Monsanto Donates Its Share of Golden Rice*, 289 SCI. 843 (2000) (detailing the introduction of genes necessary to synthesize vitamin A into rice to combat malnutrition in economically undeveloped countries).

3. *See* U.S. DEPARTMENT OF COMMERCE, U.S. INDUSTRY AND TRADE OUTLOOK § 11-14 (1999).

4. ALBERTS, ET AL., *supra* note 1, at 291-321.

5. *See id.* DNA consists of a "sequence," or linear chain, of nucleotide bases. The term "genome" refers to the total genetic information contained in an organism. *Id.* at G-10.

6. *See* Elizabeth Pennisi, *Finally, the Book of Life and Instructions for Navigating It*, 288 SCI. 2304 (2000).

7. *See id.*; *see also* Eliot Marshall, *The Patent Office Faces a 90-Year Backlog*, 272 SCI. 643 (1996) (discussing patent claims to thousands of DNA sequences by Incyte Pharmaceuticals, Inc.).

nology too liberally,[8] the agency promulgated Interim Utility Guidelines in December 1999 and January 2000,[9] and then final Utility Guidelines in January 2001.[10] The PTO also developed training materials to accompany the 1999 Revised Interim guidelines.[11] While the PTO correctly bases the utility guidelines on case law, the 1999 training materials misapply the law to DNA claims. Unless the PTO substantively amends the 1999 training materials, the PTO may incorrectly apply the utility standards to DNA claims and issue a large number of patents that the courts ultimately will hold invalid.

I. BACKGROUND

DNA contains the fundamental genetic information necessary to almost all biological processes.[12] Methods of manipulating DNA offer nearly limitless possibilities for its use.[13] To take advantage of DNA technology, high-profile research efforts have focused on sequencing large numbers of DNA sequences.[14] Such methods have become possible due to advances in the life sciences. To fully appreciate the issues surrounding utility of DNA claims, a basic understanding of molecular biology, recombinant DNA and gene sequencing is helpful.

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8. *See* Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶1 "Written Description" Requirement, 64 Fed. Reg. 71,427, 71,427-37 (Dec. 21, 1999) [hereinafter 1999 Revised Interim Guidelines].

9. *Id.*; Revised Interim Utility Examination Guidelines, 65 Fed. Reg. 3425 (Jan. 21, 2000) (adding the word "Interim" to the title and correcting a typographical error; no other changes were made).

10. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001) [hereinafter 2001 Utility Guidelines].

11. United States Patent and Trademark Office, *Revised Interim Utility Guidelines Training Materials* (Jan. 21, 2000), *available at* http://www.uspto.gov/web/menu/utility.pdf [hereinafter *1999 Training Materials*]; As of the time of publication of this Note, the PTO has not released training materials to accompany the 2001 Utility Guidelines.

12. ALBERTS, ET AL., *supra* note 1, at 10-11.

13. *Id.* at 291-292.

14. *See, e.g.*, J. Craig Venter et al., *Shotgun Sequencing of the Human Genome*, 280 SCI. 1540 (1998) (detailing the efforts of Celera, Inc. to sequence the human genome using automated sequencing technology).

A. Molecular Biology and Recombinant DNA

1. Molecular Biology

The human body consists of cells having a variety of functions arranged into multiple organ systems.[15] While different cells in different organ systems play vastly different biological roles, the majority of cells have the same fundamental biochemical structure and contain the same genetic material.[16] Many different types of molecules, including DNA, ribonucleic acid (RNA), and proteins, play a fundamental role in cellular function.[17]

Genes, the functional units of heredity, are composed of DNA.[18] DNA consists of two complementary strands, each containing a series of four nucleotide bases.[19] The complementary strands hybridize, or lock together, to form a double helix.[20] A specific, ordered sequence of bases in a DNA strand identifies a particular gene.[21]

Genes control the biochemical function of cells by serving as blueprints for protein synthesis.[22] During protein synthesis, cells first transcribe, or copy, the specific DNA sequence of a gene into a carrier material called messenger RNA ("mRNA").[23] The mRNA acts as a template for protein synthesis.[24] The portion of mRNA serving as a template for functional proteins is called an open reading frame.[25]

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15. ALBERTS, ET AL., *supra* note 1, at 28-34.
16. *See id.* at 41.
17. *Id.* at 98-127.
18. BENJAMIN LEWIN, GENES VI 71-72 (1997).
19. *Id.* at 76-82. The four bases making up DNA are adenine (A), thymidine (T), guanine (G), and cytosine (C). Scientists represent a DNA sequence by listing the series of bases contained therein. *Id.*
20. *Id.* at 86-87.
21. *Id.*
22. *See* ALBERTS, ET AL., *supra* note 1, at 104-05. Proteins direct or influence almost every cellular function. Structurally, proteins consist of a series of distinct chemicals, called amino acids, joined end to end. The chain of amino acid folds into a three dimensional conformation that effects protein function. Thus, the specific amino acid sequence of each protein determines its biochemical properties. *Id.* at 111-30.
23. *Id.* at 104-05.
24. *See* LEWIN, *supra* note 18, at 88-225. A gene includes not only the DNA sequence encoding protein amino acids (exons), but also non-coding DNA sequences (introns) and regulatory regions. After a DNA sequence is translated to produce mRNA, specific enzymes splice mRNA to remove non-coding "intron" regions leaving the portion of the gene that encodes the functional protein. The spliced mRNA serves as the template for translation, during which amino acids are joined end-to-end based on the mRNA sequence. In an open reading frame, a three base "start codon" defines where

2. *Recombinant DNA*

Recombinant DNA methods allow scientists to manipulate and study identified genes and their corresponding proteins.[26] For example, DNA sequences that encode functional proteins can be introduced into bacteria to produce massive amounts of the protein.[27] Scientists can then use the protein in a method of treatment or to identify potential therapies.[28] In addition, identification of the DNA sequences that cause genetic diseases allows rapid diagnosis of those diseases, as well as the development of novel therapies.[29] Recombinant DNA technology in agribusiness has led to the introduction of essential nutrients into staple crops in third world countries.[30] Recombinant DNA technology thus provides enormous power to improve the quality of life throughout the world.

3. *Genome Sequencing*

The DNA sequences of each cell provide all the genetic information necessary to understand how an organism functions, and recombinant methods provide the means for manipulating genetic material toward productive ends.[31] At the beginning of the 1990s, however, the majority of the DNA sequences of almost every organism remained unknown.[32] To tap the vast potential of undiscovered genetic material, both public and private entities began massive DNA sequencing efforts.[33]

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translation of mRNA to protein begins, and a three base "stop codon" defines where translation of mRNA to protein ends. *Id.*

25. *See id.* at 86, 204. An open reading frame, or sequence encoding a protein, defines the DNA sequence bounded by start and stop codons. *Id.*

26. *See* ALBERTS, ET AL., *supra* note 1, at 291-331. Recombinant DNA technology includes methods of cleaving, or breaking, DNA at specific sites using restriction enzymes, sequencing isolated DNA molecules, identifying specific DNA or RNA sequences by hybridization to complementary DNA sequences, cloning a single DNA molecule and copying it in a rapidly replicating organism such as bacteria, and designing modified versions of genes. *Id.*

27. *See id.*

28. *Id.* at 320-21.

29. *See* Eric S. Landers & Robert A. Weinberg, *Genomics: Journey to the Center of Biology*, 287 SCI. 1777 (2000) (reviewing the progress and potential of gene-sequencing efforts).

30. *See* Normile, *supra* note 2.

31. *See* ALBERTS, ET AL., *supra* note 1, at 291.

32. *See* Landers & Weinberg, *supra* note 29, at 1777.

33. Pennisi, *supra* note 6, at 2304-05; *see also* Venter et al., *supra* note 14; *see also* Li Hui, *China, Denmark Team Up to Tackle the Pig*, 290 SCI. 913 (2000); Gretchen Vogel, *Sanger Will Sequence Zebrafish Genome* 290 SCI. 1671 (2000).

Many sequencing projects have focused on obtaining the DNA sequences of entire organisms.[34] The full genome sequence of an organism allows scientists to characterize how different genes interact with each other, as well as how organisms regulate the expression of specific genes.[35] By the year 2001, scientists had already sequenced the genomes of a number of different organisms.[36] Most notably, the publicly funded Human Genome Project and the privately funded Celera, Inc., jointly announced that they independently had completed sequencing the human genome.[37]

Other DNA sequencing strategies have focused on identifying and characterizing the portion of the genome that encode proteins.[38] These efforts focus on characterizing the sequences of mRNA transcripts.[39] Since mRNA transcripts correspond to the small portion of the genome that encodes proteins, isolating and sequencing mRNA allows researchers to focus on regions of the genome important for cell function.[40] mRNA sequences can then be converted to DNA, which researchers can easily manipulate using recombinant DNA methods.[41]

4. Patenting the Human Genome

Patent applications claiming DNA sequences may have reached an unmanageable critical mass at the PTO. For example, Incyte Pharmaceuti-

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34. *See, e.g.*, Pennisi, *supra* note 6, at 2304.

35. *See* LEWIN, *supra* note 18, at 1131-72. Cells closely regulate gene expression (the production of proteins by genes). Disruption of regulatory mechanisms can result in genetic disorders such as cancer. *Id.*

36. *See* Landers & Weinberg, *supra* note 29, at 1782.

37. *See* Pennisi, *supra* note 6.

38. *See* Mark D. Adams et al., *Sequence Identification of 2,375 Human Brain Genes*, 355 NATURE 632 (1992) (describing more rapid identification of expressed sequence tags (portions of expressed genes) by the National Institute of Health).

39. *See generally* LEWIN, *supra* note 18, at 629-630. mRNA serves as a copy of the portion of DNA that encodes proteins. Therefore, isolating the mRNA allows researchers to isolate the portion of DNA controlling biochemical processes in an organism. To exploit these sequences, researchers first isolate mRNA, then convert it to more stable DNA. After isolating the total mRNA in a cell, researchers convert mRNA to more stable complementary DNA, or cDNA. cDNA is a copy of DNA encoding a protein. When the cDNA sequence only includes a portion of a functional gene, the cDNA is called an expressed sequence tag ("EST"). A large number of cDNAs derived from a single source, called a cDNA library, contain all expressed DNA in a specific source. By sequencing the cDNAs in a library, specific genes encoding a functional protein can be identified and characterized. *Id.*

40. *Id.*

41. *Id.*

cals alone has filed over 400,000 patent applications[42] claiming expressed sequence tags ("ESTs").[43] Without specific guidance as to the proper utility standards for DNA compositions, large numbers of incorrectly examined patents may issue.

B. Patentability of DNA and the Utility Requirement

The ability to obtain a large number of DNA sequences at low cost has resulted in an explosion of patent applications for DNA sequences.[44] Patents grant to an inventor the right to exclude others from making or using a claimed invention.[45] The ability to exclude others from using patented DNA sequences would allow the patent holder to control results of downstream research using the DNA sequence.

1. Statutory Patentability Requirements

Like all patent applicants, inventors claiming DNA compositions must meet the statutory patentability requirements to obtain a patent. Patent claims must demonstrate utility,[46] novelty,[47] and nonobviousness,[48] as well as enable[49] and fully describe the invention.[50] While Congress has enacted some statutory provisions specific to biotechnology, statutory patent requirements for biotechnology remain essentially the same as for other inventions.[51]

2. The Utility Requirement and Chemical Compositions

Section 101 of the Patent Act sets forth the statutory basis for the utility requirement:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore.[52]

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42. Marshall, *supra* note 7, at 643.

43. *See supra* text accompanying note 39.

44. *See, e.g.*, Marshall, *supra* note 7.

45. U.S. CONST. art. I, § 8, cl. 8 (expressly providing Congress with the power to grant inventors "the exclusive right to their . . . discoveries").

46. 35 U.S.C. § 101 (1994).

47. *Id.* § 102.

48. *Id.* § 103.

49. *Id.* § 112.

50. *Id.*

51. *See id.* § 103(b) (precluding the rejection of process claims regarding the use or making of certain nonobvious compositions specific to biotechnology).

52. *Id.* § 101.

Courts have long held that an invention must have some beneficial use to society to satisfy the utility requirement.[53] The threshold "beneficial use" remains low, however, providing that a claimed invention need not perform functions more effectively than similar inventions or technologies.[54] Courts generally allow the market to determine whether an invention actually benefits society more than already existing technologies.[55]

Beginning in 1950, the court expanded this de minimis view of the utility requirement for chemical compositions with known chemical structure, but only for speculative or hypothetical use. In *In re Bremner*, an applicant claimed a new chemical composition, but failed to assert any specific use for the composition.[56] The court found the claimed invention unpatentable, holding that an application must disclose some specific use for the compound to satisfy the utility requirement.[57] Although the *Bremner* court required an assertion of utility for a claimed invention, the substantive utility requirements remained low.[58]

In *Brenner v. Manson*, the U.S. Supreme Court explicitly narrowed the utility requirements for inventions, particularly chemical compositions, having only hypothetical utilities.[59] In *Manson*, a patent claiming a steroid composition failed to articulate any use for the steroid but specified that other steroids having similar chemical structure had well-established utility.[60] The Court held that the experimentally established utility of a homolog, or chemical variant, of a claimed chemical compound failed to establish the utility of the claimed compound, since minor variations in

53. *See, e.g.*, Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C. Mass. 1817) (No. 8565) holding that a patent meets the utility requirement so long as it is not "frivolous or injurious to the well-being, good policy, or sound morals of society"); *see also* Bedford v. Hunt, 3 F. Cas. 37, 37 (C.C. Mass. 1817) (No. 1217) (holding that the law requires an invention to be "capable of use, and that the use is such as sound morals and policy do not discountenance or prohibit it").

54. *See Lowell*, 15 F. Cas at 1019 (stating that if an invention is less useful than other, similar inventions, "it will silently sink into contempt and disregard").

55. *Id.*

56. *In re* Bremner, 182 F.2d 216, 216 (C.C.P.A. 1950).

57. *Id.* at 217.

58. In *In re Nelson*, 280 F.2d 172 (C.C.P.A. 1960), the court briefly appeared to back away from some implications of the *Bremner* decision. The *Nelson* court held an asserted utility of a claimed compound as a starting material in the synthesis of a class of steroids, at least some of which had therapeutic use, sufficient to establish utility. *Id.* at 180. *But see In re* Kirk, 376 F.2d 936, 945 (C.C.P.A. 1967) (holding that *Brenner v. Manson* 383 U.S. 519 (1966) essentially overruled *Nelson*).

59. 383 U.S. at 536.

60. *Id.* at 533-34.

chemical structure could result in large changes in biochemical function.[61] The Court further held that a claimed invention must have a "specific" and "substantial" practical utility.[62] While a patent must assert utility specific to the claimed invention,[63] the *Manson* court did not specify the requisite degree of use necessary to establish "substantial" utility.[64]

Subsequent cases have held that an unspecified general biological utility of a chemical compound fails to meet the required utility standard.[65] The credible assertion that a claimed compound can treat a specific disease, such as cancer, however, satisfies the utility requirement.[66] Courts have continued to define "practical utility" as "specific" and "substantial" utility,[67] and to hold that practical utility attributes "real-world value" to a claimed invention.[68] For pharmaceutical inventions, the assertion of utility as a treatment method combined with in vitro data generally satisfies the requirement for "practical utility."[69]

Courts have also extended the *Manson* decision to chemical compositions useful as intermediates in synthesizing a separate final product. In *In re Joly*, the court held that an applicant must assert some utility for the final product of the claimed intermediate to satisfy the utility requirement.[70] The court further held that the specific and substantial practical utility of the final product is an essential element in establishing the utility of an intermediate.[71]

The Federal Circuit most recently revisited the utility requirement in *In re Brana*.[72] In *Brana*, the applicant claimed a chemical composition and asserted that the compound could be used as an anti-tumor treatment.[73] The applicant supported this assertion in the patent specification by indi-

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61. *Id.* at 532-33.

62. *Id.* at 534.

63. *Id.*

64. *Id.* at 535.

65. *See In re* Kirk, 376 F.2d 936, 945 (C.C.P.A. 1967).

66. *See In re* Brana 51 F.3d 1560, 1565 (Fed. Cir. 1995) (distinguishing *In re Kirk* since the Brana application asserted specific utility of the compound directed to the treatment of a certain type of cancer).

67. *See, e.g., In re* Ziegler, 992 F.2d 1197, 1201 (Fed. Cir. 1993).

68. *See, e.g.*, Nelson v. Bowler, 626 F.2d 853, 856 (C.C.P.A. 1980).

69. *See* Cross v. Iizuka, 753 F.2d 1040, 1048 (Fed. Cir. 1985) (holding that the in vitro tests are sufficient to establish the utility of pharmaceuticals under appropriate circumstances).

70. *In re* Joly, 376 F.2d 906, 908 (C.C.P.A. 1967).

71. *Id.* (quoting *In re* Kirk, 376 F.2d 936, 945 (C.C.P.A. 1967)).

72. 51 F.3d 1560 (Fed. Cir. 1995).

73. *Id.* at 1562.

cating that the compound showed promise in in vitro tumor cell models.[74] The Board of Patent Appeals and Interferences ("Board") upheld the rejection, but the Federal Circuit reversed the Board.[75] The Federal Circuit held that the PTO had failed to prove the prima facie burden for lack of utility.[76] Since an assertion that the compound had anti-tumor properties was a specific practical use and the claimed compound had better action in vitro than known anti-tumor drugs, the Federal Circuit held that the PTO had not demonstrated that a person of ordinary skill in the art would not believe that the claimed compound was an anti-cancer agent.[77]

While no court has yet ruled directly on the utility of DNA compositions, the Board has indicated that the practical utility standards apply to biotechnology patents. In *Ex parte Maizel*, the Board held that the lack of an asserted use for a claimed growth factor protein, while not an issue in controversy, may have indicated that the protein lacked practical utility.[78] In *Ex parte Deuel*, the Board questioned whether a DNA sequence derived from rat was sufficiently homologous to human DNA to be used as a probe for similar DNA sequences.[79]

II. THE UTILITY GUIDELINES AND TRAINING MATERIALS

While the courts determine how statutory requirements apply to cases in controversy, the PTO serves as the first line of review for patent applications. To ensure that patent examination comports with statutory patentability requirements and case law, the PTO devised a series of guidelines specific to different statutory requirements.[80] The PTO first released utility guidelines in 1995.[81]

In December 1999 and January 2000, the PTO released Revised Interim Utility Guidelines in response to criticism that the PTO examined

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74. *Id.* at 1563 n.3.

75. *Id.* at 1562.

76. *Id.* at 1563.

77. *Id.* at 1565.

78. *Ex parte* Maizel, 27 U.S.P.Q.2d (BNA) 1662, 1668 (Bd. Pat. App. & Int'f 1992).

79. *Ex parte* Deuel, 27 U.S.P.Q.2d (BNA) 1360, 1365 (Bd. Pat. App. & Int'f 1993), *overruled by In re* Deuel, 51 F.3d 1552, 1560 (Fed. Cir. 1995) (while overruling the Board on the obviousness issue, the Federal Circuit left open further review by the PTO on other statutory grounds, including utility).

80. Guidelines for Examination of Applications for Compliance With the Utility Requirement, 60 Fed. Reg. 36,263 (July 14, 1995) [hereinafter 1995 Utility Guidelines].

81. *Id.*

biotechnology patents too liberally.[82] After receiving public comments on the interim guidelines, the PTO promulgated final Utility Examination Guidelines in January 2001.[83] The 2001 Utility Guidelines supersede the Revised Interim Utility Examination Guidelines.[84]

The 2001 Utility Guidelines require that a claimed invention either have a well-established utility or assert a specific, substantial, and credible utility.[85] In addition, the guidelines state that an invention should not be rejected for lack of utility if the claim has a well-established utility.[86] The PTO should determine whether the claimed invention asserts a particular practical utility, defined as a specific and substantial use that one skilled in the art would consider credible.[87] The guidelines state that the requirement of specific and substantial utility "excludes throw-away, insubstantial, or nonspecific utilities, such as the use of a complex invention as landfill."[88] To reject an application on utility grounds, the PTO must establish a prima facie lack of utility by a preponderance of the evidence and allow applicants to rebut the prima facie showing.[89] The 2001 Utility Guidelines also caution that PTO personnel must presume that statements by applicants are true unless evidence shows that one of ordinary skill in the art would have legitimate basis to doubt the credibility of the applicant's statement.[90]

The PTO developed training materials corresponding to the 1999 Revised Interim Guidelines.[91] The 1999 training materials define standards used in the guidelines and provide specific examples of applying the

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82. 1999 Revised Interim Guidelines, *supra* note 8, at 71,441 (In the commentary preceding the 1999 Revised Interim Guidelines, the PTO argued that some criticism of biotechnology examination standards would be better addressed by the utility requirement.).

83. 2001 Utility Guidelines, *supra* note 10, at 1098. The 2001 Utility Guidelines revise the 1999 Revised Interim Guidelines to clarify that (1) an examiner should reject a claim for lack of utility "where an applicant has not asserted a specific, substantial, and credible utility, and the examiner does not perceive a well-established utility" and (2) "evidence provided by an applicant is to be analyzed with regard to a concordance between the showing and the full scope and content of the claimed invention as disclosed in the application as filed." *Id.* at 1096.

84. *Id.* at 1092.

85. *Id.* at 1098.

86. *Id.*

87. *Id.*

88. *Id.*

89. *Id.*

90. *Id.* at 1098-99.

91. *1999 Training Materials*, *supra* note 11. As of the time of publication of this Note, the PTO has not yet released training materials associated with the 2001 Utility Guidelines.

guidelines to different claimed inventions.[92] The training materials define a *credible* utility as one that a person of ordinary skill in the art would believe.[93] The application must also disclose *specific* utility to the claimed subject matter, as opposed to a general utility for the broad class of inventions.[94] Finally, the training materials require that a claimed invention have a *substantial* utility that defines a "real world use."[95] If claims fail to establish the requisite utility, the PTO should reject them on both utility and enablement grounds.[96]

Examples presented in the 1999 training materials focus almost exclusively on biotechnology patent claims.[97] Of the examples provided by the training materials, twelve of thirteen apply to biotechnology, and two focus on DNA compositions.[98] Of those, one applies to DNA fragments and the other focuses on DNA fragments containing a full open reading frame potentially capable of producing a protein by recombinant methods.[99]

Both the 2001 Utility Guidelines and the 1999 Revised Interim Utility Guidelines provide additional requirements to the previous 1995 utility guidelines.[100] The newly promulgated guidelines require that the asserted utility should be credible and satisfy both "specific" and "substantial" utility requirements.[101] The 1995 guidelines, however, required a specific utility but not substantial utility.[102]

III. DISCUSSION

The new utility guidelines may prevent inventors from seeking patent protection for speculative DNA patents in order to control subsequent research and development. The 2001 Utility Guidelines correctly restate the utility requirement according to established case law. In the training materials that accompanied the 1999 Revised Interim Utility Guidelines, how-

92. *1999 Training Materials*, *supra* note 11, at 5-74 (comparing credible utility to inoperable or incredible inventions such as perpetual motion machines).

93. *Id.* at 5.

94. *Id.* at 5-6.

95. *Id.* at 6.

96. *Id.* at 10 (arguing that if an application fails to establish a use, the application implicitly fails to teach one skilled in the art how to use the invention).

97. *Id.* at 13-74.

98. *Id.*

99. *Id.* at 50-55; *see also supra* text accompanying note 24.

100. *Compare* 2001 Utility Guidelines, *supra* note 10, *and* 1999 Revised Interim Guidelines, *supra* note 8, *with* 1995 Utility Guidelines, *supra* note 80.

101. 2001 Utility Guidelines, *supra* note 10, at 1098; *see also* 1999 Revised Interim Guidelines, *supra note* 9, at 71442.

102. 1995 Utility Guidelines, *supra* note 80, at 36,265.

ever, the PTO misapplies the established case law by applying utility standards outside the scope of judicial precedent. Unless the PTO substantially revises the 1999 training materials, incorrect application of the 2001 Utility Guidelines may result in the issuance of DNA patents that the courts ultimately will invalidate.

A. Patents Claiming Uncharacterized DNA Sequences Discourage Subsequent Research and Development

Commentators have argued that granting broad patent rights to DNA compositions will give the patent holder excessive control of subsequent therapeutic developments related to the gene product.[103] DNA patents grant the owner the right to exclude others from making or using the DNA. Use of a claimed DNA composition requires a license from the patent owner.[104] Thus, ownership of DNA also gives the right to control compositions, therapies, and research efforts besides the DNA composition itself.[105] Since scientists routinely use recombinant DNA to synthesize proteins, any effort to produce an unpatented protein using patented DNA would require licensing the rights to the DNA.[106] When scientists implicate a gene product in a particular pathology or disease, the ability to develop or test the efficacy of drugs affecting the protein in vitro requires a license from an owner of the DNA encoding the protein.[107]

Since automated sequencing techniques allow scientists to acquire DNA sequences at very low cost, obtaining patent rights to such DNA sequences can be extremely profitable.[108] Between 1995 and 1999, the PTO faced an exponentially increasing number of patent applications claiming DNA sequences.[109] Biotechnology corporations such as Incyte Pharmaceuticals, Inc. have filed a large number of patent applications claiming DNA compositions.[110]

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103. *See, e.g.*, Molly A. Holman & Stephen R. Munzer, *Intellectual Property Rights in Genes and Gene Fragments: A Registration Solution for Expressed Sequence Tags*, 85 IOWA L. REV. 735, 774-93 (2000) (arguing, in part, that granting patent rights to DNA fragments gives "power that decrease incentives for research on full-length genes, [and leads to] . . . underuse of genetic discoveries, . . . fractionation of licensing arrangements, and . . . downstream effects of market inefficiencies").

104. *Id.* at 776-83.

105. *Id.* at 776.

106. *Id.*

107. *Id.*

108. *Id.*

109. *See, e.g.*, Marshall, *supra* note 7.

110. *Id.*

With very valuable rights available at low cost, requiring an inventor to assert a specific, substantial, and credible utility may prevent "shotgun" sequencers, who assert only speculative utility for a putative protein, from obtaining patent protection. The 2001 Utility Guidelines may limit claims to DNA compositions having only speculative utility.

B. Judicial Precedent Supports the 2001 Utility Guidelines

The PTO promulgates examination guidelines for specific statutory patent requirements to guide patent office examination practice.[111] The agency bases the requirements on both statutory directives and court precedent.[112] PTO guidelines do not represent an attempt by the PTO to make law.[113] Rather, they constitute a means to promote consistent patent examination across general technologies and sub-species of technology.[114] The PTO therefore continues to do what it has always done: apply existing law to new technologies.

The 2001 Utility Guidelines are consistent with established case law that applies utility to chemical compositions. The guidelines specifically state that patent applications must articulate a specific and substantial practical utility as required by *Brenner v. Manson*.[115] The guidelines, however, remain sufficiently broad to accommodate a wide variety of inventions. While the PTO drafted the new utility guidelines in response to concerns related to biotechnology, the guidelines are applicable to all inventions.[116]

The guidelines correctly place the initial prima facie burden of proving a lack of utility on the PTO, and the subsequent burden on the applicant.[117] To satisfy the prima facie burden, the PTO must show that one of ordinary skill in the art would reasonably doubt the asserted utility.[118] The PTO has no duty to present evidence in every case, since unpredictability in chemi-

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111. *See* 2001 Utility Guidelines, *supra* note 10, at 1092.

112. *See id.* at 1097-98.

113. *See id.* (specifically stating that the "guidelines have been promulgated to assist Office personnel in their review of applications for compliance with the utility requirement" and "the guidelines do not alter the substantive requirements of 35 U.S.C. § 101 and § 112").

114. *Id.*

115. 383 U.S. 519, 533-34 (1966).

116. *See* 2001 Utility Guidelines, *supra* note 10, at 1097-98.

117. *See, e.g., In re* Brana 51 F.3d 1560, 1566 (Fed. Cir. 1995) (holding that the PTO must provide evidence showing "that one of ordinary skill in the art would reasonably doubt the asserted utility" before the burden shifts "to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility").

118. *Id.*

cal inventions may alone create reasonable doubt as to the accuracy of a claimed utility.[119] In cases where an invention conforms to well-known principles in the art, no additional evidence may be required.[120] The burden of rebutting the prima facie utility rejection then rests with the applicant.[121]

The guidelines also properly direct the PTO to reject claims lacking utility on both utility and enablement grounds.[122] The courts have long held that a lack of utility under § 101 also justifies a rejection under § 112.[123] If a claim asserts no use, it cannot teach one skilled in the art how to use the invention as required by § 112. Therefore, in promulgating the 2001 Utility Guidelines, the PTO does not overstep its authority and appears to apply standards consistent with case law.

C. Applying the Utility Requirement to DNA Claims

The utility requirements for DNA sequences should mirror those already developed for chemical compositions.[124] DNA sequences, like other chemical compositions, have specific chemical structures that impart specific properties.[125] Like other chemical compositions, slight variations in the chemical structure of DNA can result in large changes in activity.[126] While some DNA compositions have experimentally established functions, their utility depends on the degree to which they have a practical use defined by case law.[127]

Claims to DNA compositions vary as to whether they assert a credible practical use. While some DNA compositions have an experimentally established function, others assert a speculative function based on homology (i.e., similarity to other known sequences).[128] The asserted utility of DNA

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119. *See In re* Novak, 306 F.2d 924, 928 (C.C.P.A. 1962) (holding that a patent examiner may request additional evidence of an asserted utility unless one of ordinary skill in the art would accept the assertion).

120. *See, e.g.*, *In re* Chilowsky, 229 F.2d 457, 462 (C.C.P.A. 1956) ("Where the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is required.").

121. *See, e.g.*, Fujikawa v. Wattanasin, 93 F.3d 1559, 1563 (Fed. Cir. 1996).

122. *See, e.g.*, *In re* Brana, 51 F.3d at 1566.

123. *See id.* (citing *In re* Marzocchi, 439 F.2d 220, 223 (C.C.P.A. 1971)).

124. *See* discussion *supra* Part I.B.2.

125. *See* ALBERTS, ET AL., *supra* note 1, at 291-331.

126. *See* LEWIN, *supra* note 18, at 89-90.

127. *See* discussion *supra* Part I.B.2.

128. *See generally* Steven E. Brenner et al., *Assessing Sequence Comparison Methods with Reliable Structurally Identified Distant Evolutionary Relationships*, 95 PROCEEDINGS OF THE NAT'L ACAD. OF SCI. 6073 (1997). *See also* ALBERTS, ET AL., *supra* note 1, at G-12. The term "homology" broadly refers to "[s]imilarity in structure of [a

compositions tend to fall into two categories: (1) claims to polynucleotide sequences capable of use as probes for identical or similar sequences, and (2) claims to sequences comprising an open reading frame that encodes a putative full length protein.[129] Both cases require careful application of existing case law in evaluating whether the sequences meet the requisite standards of utility.

1. The Utility Requirement and DNA Probes

DNA probes consist of DNA sequences used to identify identical or similar sequences.[130] DNA contains two individual strands, each a series of nucleotide bases.[131] The sequence on one strand hybridizes, or sticks, to the complementary sequence on the other strand.[132] The more complementary the sequences, the stronger the hybridization.[133] By introducing a single strand of DNA (a "probe") having a specific sequence into a mixture containing unknown nucleotide sequences, scientists can identify similar sequences in the mixture based on the amount of hybridization.

DNA sequences can typically be used as probes to detect a point on a specific chromosome,[134] or to detect the presence or absence of mRNA in a specific group of cells.[135] There are few limits to the length of a DNA

DNA or protein sequence] . . . reflecting a common evolutionary origin." *Id.* at G-12. Proteins from different organisms having similar sequences can have similar biochemical functions. *Id.* at 14-15. When researchers characterize a new DNA sequence, they compare the sequence of the encoded protein with known sequences to make an educated guess as to its relationship and function. *Id.* However, the ability to identify evolutionary relationships between a claimed DNA sequence and other known sequences depends on factors such as the number of experimentally verified sequences and the accuracy of sequence identification. *See* Brenner et al., *supra*, at 6087.

129. *See, e.g.*, *1999 Training Materials*, *supra* note 11, at 50-55. The 1999 training materials provide examples of DNA sequences that either contain an open reading frame, which may be used to characterize a protein, or sequences useful as probes to identify other similar sequences. *Id.*

130. ALBERTS, ET AL., *supra* note 1, at 300-05. DNA consists of two complementary strands, each binding preferentially and specifically to its complementary sequences. One strand labeled with a radioactive or fluorescent tag can be used to probe for complementary or nearly complementary DNA sequences. *Id.*

131. *Id.*

132. *Id.*

133. *Id.* at 300.

134. *Id.* at 130. DNA compositions may be used as chromosome markers assuming that their location on the chromosome has been determined. *Id.*

135. *See id.*; *see also supra* text accompanying note 24. Since the cell first translates DNA encoding functional genes to mRNA, using a DNA probe complementary to an expressed sequence can be used to measure the amount of expressed DNA in a specific group of cells. *Id.*

sequence used as a probe; while DNA sequences must have a finite length to bind targets specifically, sequences as large as an entire genome may be used.[136]

If a patent claims a DNA probe, the specification should assert a specific and substantial utility to satisfy the utility requirement articulated by case law.[137] A DNA probe clearly has a specific and substantial utility when used to detect a known complementary target sequence. For example, a probe used to detect the level of expression for an mRNA sequence having altered expression in cancer cells should satisfy the utility requirement.[138]

The probe target, however, does not need to have a known function in order to establish a specific and substantial practical utility for the probe.[139] For instance, sequences have the requisite utility if they can be used as markers for a specific location on a specific chromosome, or to detect altered expression in a certain type of tissue or disease without a known mechanism.[140] Even if biochemical function of the probe target is unknown, a DNA should satisfy the utility requirement provided that detecting the target itself is useful.

2. *The Utility Requirement and Open Reading Frames*

Other patents on DNA compositions assert that a claimed DNA composition can produce large amounts of a protein through recombinant methods. Sequences capable of producing a protein include open reading frames, which define a region of DNA capable of synthesizing a full-length protein.[141] Claimed open reading frame sequences range from well-

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136. *See* Charles D. Laird and Brian J. McCarthy, *Magnitude of Interspecific Nucleotide Sequence Variability in Drosophila*, 60 GENETICS 303, 314 (1968) (illustrating that there is no conceptual upper limit to the length of DNA useful as a probe, since the entire genomes of two different organisms can be hybridized to detect sequence similarity).

137. *See, e.g.*, Brenner v. Manson, 383 U.S. 519, 534-35 (1966).

138. *See, e.g.*, Eric R. Fearon and Bert Vogelstein, *A Genetic Model for Colorectal Tumorigenesis*, 61 CELL 759 (1990).

139. *See In re* Cortright, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (holding that "statements that a physiological phenomenon was observed are not inherently suspect simply because the underlying basis for the observation cannot be predicted or explained"); *see also* Newman v. Quigg, 877 F.2d 1575, 1581 (Fed. Cir. 1989) ("It is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works."); Fromson v. Advance Offset Plate, Inc., 720 F.2d 1565, 1570 (Fed. Cir. 1983) ("It is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests.").

140. *See* LEWIN, *supra* note 18, at 623.

141. *See id.* at 88-225, 629; *see also* text accompanying *supra* note 39. Researchers typically first identify open reading frames from mRNA transcripts.

characterized DNA sequences having experimentally confirmed functions to DNA sequences having only hypothetical functions based on the degree of homology (sequence similarity) to sequences with known functions.[142]

For a claimed open reading frame DNA sequence to satisfy the utility requirement, the protein encoded by the DNA sequence should assert a specific and substantial utility.[143] Open reading frames function essentially as de facto intermediates in protein synthesis.[144] Like steroid compounds used as intermediates to synthesize a final compound, the utility of DNA intermediates depends on the utility of the final protein. The ability to produce a protein does not necessarily satisfy the utility requirement because the protein sequence may not have any known use.

Open reading frames vary widely in the degree to which their encoded proteins assert a credible specific and substantial utility. At one extreme, DNA sequences encoding proteins having experimentally verified function and use satisfy the utility requirement.[145] At the other extreme, the function of an unknown protein can be hypothesized based on sequence similarity, or homology, to known sequences with known function.[146]

The determination of utility based on homology to known sequences goes straight to the heart of many speculative DNA claims. To demonstrate a lack of utility for a claimed DNA composition homologous to sequences having experimentally verified function, the PTO must establish that one of ordinary skill in the art would reasonably doubt the asserted utility on its face.[147] According to case law, a claimed composition used as an intermediate fails to satisfy the utility requirement if the final product bears structural similarity to chemical compounds with unknown function.[148] Unlike the chemical compositions at issue in *In re Brana*, asserted utilities based on chemical similarity frequently have not been tested in vitro. In addition, the Board has suggested that a DNA sequence having an asserted utility based solely on homology to other similar sequences fails to satisfy the utility requirement.[149] Scientific studies suggest that asser-

142. *See* Brenner, *supra* note 128, at 6073.

143. *See* Brenner v. Manson, 383 U.S. 519, 534-35 (1966).

144. See LEWIN, *supra* note 18, at 88-225.

145. In this case, the claimed invention has been reduced to practice.

146. *See, e.g.*, Brenner, *supra* note 128.

147. *See, e.g., In re* Chilowsky, 229 F.2d 457, 462 (C.C.P.A. 1956) ("Where the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is required.").

148. *See, e.g., In re* Joly, 376 F.2d 906, 908 (C.C.P.A. 1967).

149. *See Ex parte* Deuel, 27 U.S.P.Q.2d (BNA) 1360, 1365 (Bd. Pat. App. & Int'f 1993), *overruled by In re* Deuel, 51 F.3d 1552 (Fed. Cir. 1995) (while overruling the

tions of specific function based on homology can have limited predictive value and are often case specific.[150] Due to the unpredictability of determining function based on homology, DNA sequences containing open reading frames[151] may fail to satisfy the utility requirement in the absence of either exceedingly close sequence homology or experimental evidence.[152]

D. The Revised Interim Utility Training Materials

As of the time of publication of this Note, the PTO has not yet published training materials to accompany the 2001 Utility Guidelines. The training materials developed for the 1999 Revised Interim Utility Guidelines, however, indicate that the PTO might misapply judicial precedent. Despite abundant, longstanding case law directed to chemicals having known structures but only speculative utility, the training materials fail to make a direct comparison of the utility requirements for DNA compositions to the utility requirements established for other biochemical compositions.

The 1999 interim utility training materials provide two examples of how the PTO should apply the utility guidelines to DNA claims.[153] The first example presents claimed DNA sequence fragments from a cDNA library containing no open reading frame, while the second presents a claimed sequence fragment containing an open reading frame.[154] In both examples, the PTO misapplies case law involving chemical compositions to claims to DNA compositions.

Board on the obviousness issue, the Federal Circuit left open further review by the PTO on other statutory grounds including utility).

150. *See* Brenner, *supra* note 128, at 6078 (providing a systematic study of search algorithms for homologs (sequences derived from a common ancestor)). The study concludes:

> even the best database searching procedures tested fail to find the large majority of distant evolutionary relationships at an acceptable error rate. Thus, if the procedures assessed here fail to find a reliable match, it does not imply that the sequence is unique; rather, it indicates that any relatives it might have are distant ones.

Id.

151. *See supra* text accompanying note 25.

152. *See id.*

153. *See 1999 Training Materials*, *supra* note 11, at 50-55.

154. *See* LEWIN, *supra* note 18, at 88-225, 629; *see also supra* text accompanying notes 24, 26, 39.

1. Misapplication of the Utility Requirement to DNA Probes

Example 9 of the training materials presents a hypothetical patent application claiming DNA fragments derived from full-length, functional genes.[155] The hypothetical application asserts that the DNA fragments are useful as probes[156] to detect the full-length genes.[157] The PTO argues that the claimed DNA composition lacks specific utility since the probe target remains undefined, and lacks substantial utility because the target sequences have no known mechanism.[158]

The PTO incorrectly requires the probe target to have a known mechanism. Instead of requiring a probe to have specific, substantial, and credible utility consistent with case law, the PTO focuses on whether the applicant understands the biochemical mechanism of the probe target.[159] The Federal Circuit, however, has ruled that inventors need not disclose the mechanism by which an invention works, as long as the invention has a use.[160] By requiring the targets of DNA probes to have a known mechanism, the PTO would reject claims to DNA fragments for the wrong reasons.

Despite this error, the DNA fragments in Example 9 would still probably fail to establish a specific and substantial practical utility. Example 9 discloses that the claimed DNA fragments may be used for detecting the functional, full-length genes of which they are a part.[161] In *In re Kirk*, however, the Federal Circuit held that a claimed invention must be useful for more than further research on itself.[162] The probes probably fall into this category, since their only disclosed use is for further research on the genes that include them. Thus, the claimed DNA fragments described in the training materials would probably fail to satisfy the utility requirement.

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155. *1999 Training Materials*, *supra* note 11, at 50-53.

156. *See supra* text accompanying note 128.

157. *1999 Training Materials*, *supra* note 11, at 50-53.

158. *Id.*

159. *See id.*

160. *See, e.g.*, *In re* Cortright, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (holding that the disclosure of how a cure for baldness works is unnecessary to demonstrating its utility).

161. *See, e.g.*, *In re* Joly, 376 F.2d 906, 908 (C.C.P.A. 1967) (holding, in part, when a chemical composition acts as an intermediate in the production of a final product whose only asserted use is for further research, the utility requirement is not satisfied).

162. *In re* Kirk, 376 F.2d 936, 938 (C.C.P.A. 1967). *Compare In re* Brana, 51 F.3d 1560, 1565 (Fed. Cir. 1995) (holding that *In re* Kirk was distinguishable since it contained only a very general asserted utility and had no correlation to experimental observation).

2. *Misapplication of the Utility Requirement to Open Reading Frames*

Example 10 of the 1999 Training Materials presents a hypothetical patent application claiming a DNA sequence useful in producing a protein by recombinant methods.[163] The specification discloses that the DNA sequence encodes a protein sequence with 95% homology[164] to ligase enzymes having experimentally determined functions, and 50% homology[165] to alpha-actin proteins having experimentally determined function.[166] The training materials posit that a DNA sequence having high sequence homology to a known DNA sequence satisfies the utility requirement, since the DNA sequence would have a utility that is well-known in the art.

The PTO incorrectly asserts that 95% homology to known ligases sufficiently establishes a well-known utility. While ligases have a well-known general function in biotechnology, the function of the specifically claimed sequence in the example lacks experimental identification.[167] In addition, individual ligases differ markedly in their target sequences.[168] The PTO, therefore, relieves itself of the obligation to consider whether assertions of utility based entirely on homology have the specific and substantial utility required by established case law.[169]

Instead of asserting that sequences with homology to known sequences have well-established utility, the PTO should consider whether the utility of the claimed sequence establishes the threshold specific and substantial practical utility required by the courts. Homology as a concept can be an aid in determining the possible function of a newly discovered gene sequence, since proteins with similar sequences frequently function in similar ways.[170] Small differences between similar sequences can have signifi-

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163. *1999 Training Materials*, *supra* note 11, at 53-55.

164. *See supra* text accompanying note 128.

165. *Id.*

166. *See* JAMES DARNELL ET AL., MOLECULAR CELL BIOLOGY 456-57, 876-80 (2d ed. 1990). Ligases are specific proteins that link two ends of a DNA molecule together. *Id.* at 456-57. Actins are proteins involved in muscle contraction and extra-cellular adhesion. *Id.* at 876-80.

167. *1999 Training Materials*, *supra* note 11, at 53-55.

168. *See* DARNELL ET AL., *supra* note 166, at 456-57.

169. If the asserted utility is well-established in the art, then there is no reason to determine whether it is specific or substantial. Yet according to the facts of the provided example, the utility of the putative protein product is not well-known, since it has never been produced and measured.

170. *See* ALBERTS, ET AL., *supra* note 1, at 35 (discussing how proteins from evolutionarily related organisms have varying sequences with the same function).

cant differences in biological activity.[171] In addition, even proteins with highly similar sequences can have markedly different functions.[172] In practice, the assertion of specific utility based entirely on homology would generally be regarded by one of ordinary skill in the art as an extremely limited predictor of actual function.[173] By failing to address the limitations of homology arguments, however, the PTO risks granting patents that the courts may subsequently invalidate for lack of utility.

3. Public Comments on the Utility Requirement

While the PTO has not yet published training materials to accompany the January 2001 Utility Guidelines, the agency responded to criticism of the 1999 Revised Interim Utility Guidelines and associated training materials, including criticism concerning the validity of sequence homology in establishing utility.[174] The PTO responses indicate that the agency will not allow or reject claims to DNA sequences per se based on homology to characterized sequences.[175] Rather, the PTO states that it must meet its prima facie burden depending on the facts of each case.[176] In light of the case law and scientific criticism concerning the reliability of basing assertions of utility on sequence homology, new training materials should provide guidance to examiners as to threshold requirements for rejecting claims to DNA sequences in patent applications.

IV. CONCLUSION

Congress vests the PTO with the unenviable job of anticipating how the courts will decide cases involving new technologies. While the utility guidelines require higher utility standards for DNA claims, the training materials accompanying the 1999 Revised Interim Utility Guidelines suggest that the PTO may apply the guidelines without reference to closely analogous case law on speculative biochemical compositions. The new utility guidelines may limit the extent to which "shotgun cloners" can control downstream research on gene-products and the use of DNA. Unless the PTO revises the 1999 training materials, however, the agency still may issue a large number of patents that the courts ultimately will hold invalid.

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171. *See* LEWIN, *supra* note 18, at 89-93 (showing how acquired mutations in DNA can result in observable differences in the function of the protein encoded by the gene).

172. *See id.*

173. *See* Brenner, *supra* note 128 and accompanying text. Assessing the limits of homology in the context of DNA sequences lies beyond the scope of this Note.

174. 2001 Utility Guidelines, *supra* note 10, at 1096-97.

175. *Id.* at 1096.

176. *Id.*