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RESOLVING THE DILEMMAS BETWEEN THE PATENT LAW AND BIOTECHNOLOGY: AN ANALYSIS OF THREE RECENT BIOTECHNOLOGY PATENT CASES

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I. INTRODUCTION

Biotechnology is broadly defined to “include any technique that uses living organisms (or parts of organisms) to make or modify products to improve plants or animals or to develop microorganisms for specific use.”1 Recombinant DNA technology, a branch of biotechnology, essentially involves isolating and replicating a genetic material, such as a desired gene, from one species and inserting the gene into cells of another species (“host cells”).2 The “transformed” host cells may then be capable of producing a protein encoded for the foreign gene.3 Recombinant DNA technology makes it possible to produce proteins having therapeutic effects in marketable quantities for treatments of diseases.

In 1980 the U.S. Supreme Court handed down a landmark decision allowing a patent for a live, human-made, and genetically-engineered bacterium in Diamond v. Chakrabarty,4 marking the beginning

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1. For a review of basic principles of molecular biology, see James D. Watson, Molecular Biology of the Gene (4th ed. 1988). See also infra note 28 and accompanying text.

2. See Peter R. Wheale and Ruth M. McNally, Genetic Engineering: Catastrophe or Utopia? 25-38 (1988); see infra note 28 and accompanying text; see generally John D. Hawkins, Gene Structure and Expression (1985). Deoxyribonucleic acid (DNA) is composed of four nucleotide bases, Adenine(A), Thymine (T), Cytosine (C), and Guanine (G). DNA is a basic form of storing genetic information. Three of the four nucleotide bases constitute a genetic code, called codon, which may be transcribed into corresponding ribonucleic acids (RNAs), which encode for and are translated into an amino acid. Different combinations of the four nucleotide bases form various codons which result in today’s variations of genetic traits between and among species. A gene is a functional unit of DNA. Id. at 10.

3. See infra note 28 and accompanying text.

4. 447 U.S. 303 (1980). Chakrabarty’s invention was a genetically-engineered bacterium capable of breaking down multiple components of crude oil. Id. at 305. During the examination of the patent application, the patent examiner rejected the patent claim for the bacterium, relying

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of a biotechnology era. Since then, the biotechnology industry has been booming. The number of biotechnology companies in the U.S. increased from 93 before 1970 to about 1,330 in 1994. World-wide annual sales of biotechnology-derived products had grown from zero in 1980 to $5.9 billion in 1992 to $7.0 billion by 1993. Sales in the biotechnology industry have been projected to reach $50 billion in the United States by the year of 2000.

The biotechnology industry in the U.S. has infused 23 new drugs into the market and holds close to 300 drugs awaiting regulatory approval. Likewise, biotechnology has made enormous impacts in agriculture, environmental protection, and other fields. Biotechnology has improved crops’ resistance to diseases, pests, drought, and frost. Genetically engineered microorganisms can help to restore contaminated soil and water.

Despite the appealing prospects, investments in the biotechnology industry are a high risk and high cost venture. It normally takes 10 to 12 years and $259 million (per product) to develop a biotechnology-derived product and bring it to the market. Because of the cut

on the ground that microorganisms are “product[s] of nature.” Id. at 306. The U.S. Supreme Court disagreed and found that Congress intended the patentable subject matters to “include anything under the sun that is made by man.” Id. at 309.


6. Hearing on the Competitiveness of the U.S. Biotechnology Industry Before the Subcomm. on Science, Technology, and Space of the Senate Comm. on Commerce, Science, and Transportation, 103rd Cong., 2nd Sess. 18, 29 (1994). [Hereinafter, Hearing on the Competitiveness of the U.S. Biotechnology Industry] (Senator Burns briefly described the history of development in the biotechnology industry. Ms. Lisa Conte, President and Chief Executive Officer (CEO) of Shaman Pharmaceuticals, testified before the Subcommittee. Ms. Conte presented detailed statistics on the numbers and types of the biotechnology companies in the U.S.. Out of the 1,300, there are 525 biotherapeutic companies, 344 diagnostic companies, 191 agriculture-biotechnology companies, and about 100 firms in the chemical and environmental segments.)


9. Hearing on the Competitiveness in the U.S. Biotechnology Industry, supra note 6, at 3. (Senator Hollings commented on the industry.)

10. Id.
11. Id.
12. Id.
13. Id. at 2. (Senator Burns’s comments.)
ting-edge nature of the industry, it is estimated that only 5 out of 4,000 compounds tested in preclinical trials make it to human testing.\(^\text{14}\) Only one of those five compounds tested in humans is approved for sale.\(^\text{15}\) In fact, less than one percent of the biotechnology companies are profitable, and the industry as a whole has never had a profitable year.\(^\text{16}\) For the aforementioned reasons, investors in the biotechnology industry have to be assured that their long-term interests are protected. Biotechnology patenting is a means to protect the fruits of biotechnological inventions and the underlying investments.

Patent law is considered to play a very important role in the development of biotechnologies because a patent offers to patent owners great economic incentives and benefits derived from the monopoly power during a patent term.\(^\text{17}\) Patents for new products or innovations resulting from recombinant DNA technology have issued in a wide variety of areas, such as health care, environmental protection, and agriculture. For example, patents have issued for bacteria, into which foreign genes capable of degrading oil and other toxin have been introduced,\(^\text{18}\) and for agricultural pesticidal bacteria.\(^\text{19}\) Patents have also issued for biological products, such as a protein called tissue plasminogen activator ("t-PA"), which can dissolve clots in blood vessels and has a therapeutic effect on heart-attack patients.\(^\text{20}\)

However, several recent court decisions, mainly from the federal district courts, on biotechnology patent disputes are likely to generate concerns in the biotechnology industry. These decisions manifest some internal friction and dilemmas between the fundamentals of pat-

\(^{14}\) Hearing on the Competitiveness in the U.S. Biotechnology Industry, supra note 6, at 56. (Testimony by Mr. Mark Skaletsky, CEO of GelTex Pharmaceuticals.)

\(^{15}\) Id. (Regulatory approval processes take about 7 years.)

\(^{16}\) Id. at 18. (Ms. Lisa Conte's testimony. The reasons for the industry showing consistent loss include lack of a commercialized product and high-capital allocations into research and development.)

\(^{17}\) Burk, supra note 5, at 22. A patent grants a patent owner a right to exclude others from selling, using and making the patented product. 35 U.S.C. § 271 (1952), see infra note 46 and accompanying text. See also Lynn H. Pasahow, PATENT AND TRADE SECRET BIOTECHNOLOGY LITIGATION, 886 ALI-ABA 37, 39-40 (1993). (Cetus Co., the owner of patents for polymerase chain reaction (PCR), sold the patented technology to Hoffmann-LaRoche Co. for $330 million.)

\(^{18}\) See e.g., U.S. Patent No. 4,535,061 (entitled Bacteria capable of dissimulation of environmentally persistent chemical compounds).

\(^{19}\) See e.g., U.S. Patent No. 5,002,765 (entitled Cloning and expression of Bacillus thuringiensis gene toxic to beetles of the order Coleoptera).

ent law and the application of biotechnology. Section I of this article is an introduction. Section II illustrates some basic concepts of recombinant DNA technology. Section III of this article briefly reviews the patent law concerned. In particular, this Section introduces basic principles of patent infringements and the application of the doctrine of equivalents.

Section IV discusses three patent infringement cases related to patents for biological products and the process of making the products. The first case, *Hormone Research Foundation v. Genentech, Inc.*,\(^{21}\) concerns an issue of whether an accused product, made by recombinant DNA technology, infringes patents covering a similar product is made by a conventional technology. A potential finding of infringement under the doctrine of equivalents in *Hormone Research* will prohibit anyone else from making the accused product by recombinant DNA technology. The second case, *Scripps Clinic & Research Foundation v. Genentech, Inc.*,\(^{22}\) raises a similar issue of whether an accused product, which is made by recombinant DNA technology and has better qualities, infringes patents of the same product of less purity and potency, which is made by a conventional technology.

The final case, which will be discussed extensively, is *Genentech, Inc. v. Wellcome Foundation, Ltd.*\(^{23}\) The case raises a serious issue of whether the application of the doctrine of equivalents restrains improvements of patented biological products or the processes of making the products by a third party, who is neither a patent owner or licensee. In the recent *Wellcome* decision, the Federal Circuit Court of Appeals reversed the trial court’s decision and defeated the plaintiff’s assertion of infringement under the doctrine of equivalents.\(^{24}\) The issues presented in these three cases illustrate the dilemmas in which the application of the patent law, particularly the doctrine of equivalents, may actually restrain the improvement and advancement of biotechnology. In addition, all accused products in the three cases are biotechnology-derived products which have important therapeutic effects to human diseases, some of which can be life-threatening or fatal.


\(^{24}\) *Infra* note 184 and accompanying text.
Section V discusses the dilemmas arising from the decisions surrounding the three cases and the ramifications arising from the recent *Wellcome* decision as to the methodology of analysis under the doctrine of equivalents. The Federal Circuit Court of Appeals in *Wellcome* appears to favor non-patent owner's rights in a product, which has profoundly enhanced properties other than the patented product at issue. Arguably, the recent *Wellcome* holding may have placed a heavier burden upon the plaintiffs to prove infringement under the doctrine of equivalents in biotechnology patent cases. This Section also discusses views from other commentators concerning the likely solutions to the dilemmas between patent law and biotechnology, and includes a brief comment about the real versus perceived restraining effects of the doctrine of equivalents on biotechnology.

Section VI is a conclusion. In view of the short history of biotechnology patenting, dating back to 1980, any hasty legislative or judicial modification of the patent law, particularly the doctrine of equivalents, to better fit the new and advanced biotechnology appears to be premature. In the meantime, the Federal Circuit Court of Appeals continues its endeavor of refining the methodology of analysis under the patent law, particularly under the doctrine of equivalents. The recent case law history has indicated the Federal Circuit Court has been attempting to resolve the dilemmas between the patent law and biotechnology. The recent *Wellcome* decision exemplifies such attempt. This article concludes that it is wise to allow time for the judiciary to develop a line of case law in the area of biotechnology patenting.

II. BASIC CONCEPTS OF RECOMBINANT DNA TECHNOLOGY

“Genetic engineering is the manipulation of heredity or the hereditary material.” Recombinant DNA technology has been one of several fundamental innovations in genetic engineering since World War II.

The basic technique of recombinant DNA technology involves isolating a desired gene, or a DNA fragment, and reconnecting the desired DNA to a DNA vector, which is normally a circular DNA and capable of self-replication inside host cells. The process begins with

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25. *Id.*
26. WHEALE AND McNALLY, supra note 2, at 19.
27. *Id.* at 20.
the use of one type of enzyme, called restriction endonuclease, which cuts the desired gene at specific points of the DNA sequence from cells.\textsuperscript{29} The circular DNA of the vector is also cut by the enzyme. Another enzyme, called ligase, can re-connect the cleaved desired DNA fragment with the cut vector DNA to form a recombined circular DNA.\textsuperscript{30} The recombined DNA is then introduced into host cells, such as bacterial cells, which are capable of reproducing large quantities of the desired gene's products, which are usually proteins.\textsuperscript{31} For example, a human protein, known as human Factor VIII:C, has been successfully produced in baby hamster kidney cells using recombinant DNA technology.\textsuperscript{32}

III. BRIEF REVIEW OF APPLICABLE PATENT LAW

The enactment of Patent statutes is expressly authorized by the U.S. Constitution "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to . . . Inventors the exclusive Right to their respective . . . Discoveries."\textsuperscript{33} The first Patent Act was enacted in the second session of the Congress in 1790\textsuperscript{34} and the current patent statutes are amendments based upon the Patent Act of 1951.\textsuperscript{35}

The patent system was established to fulfill two primary goals.\textsuperscript{36} First, the patent system encourages disclosure of an invention to the public because the patent statutes require a full and clear description of the invention in a specification of a patent which will be published when issued.\textsuperscript{37} In return, the patent owners are granted rights to exclude others from making, selling, and using the patented invention during the patent term.\textsuperscript{38} The current patent term for utility patents is

\textsuperscript{29} WHEALE AND MCNALLY, supra note 2, at 5.
\textsuperscript{30} BROWN, supra note 28, at 5.
\textsuperscript{31} Id. at 1-2.
\textsuperscript{32} See Scripps Clinic & Research Foundation v. Genentech, Inc., 927 F.2d 1565 (Fed. Cir. 1991), rev'd 666 F. Supp. 1379 (N.D. Cal. 1987). Human Factor VIII:C plays an important part in a blood clotting process. Thus, Factor VIII:C has a therapeutic effect on patients with hemophilia. See infra note 132 and accompanying text.
\textsuperscript{33} U.S. CONST. art I, § 8, cl 8.
\textsuperscript{34} Act of April 10, 1790, ch. 7, 1 Stat. 109 (repealed 1793).
\textsuperscript{38} 35 U.S.C. § 271(e) (1952).
seventeen years from the date of issuance. Secondly, the disclosure of an invention and the enormous benefits to patent owners will presumably stimulate more ideas and the eventual development of further significant advances in the art. In the meantime, the benefits offered to patent owners will likewise presumably foster industrial development in advanced technologies, such as biotechnology.

In order for an invention to be patentable, the invention must be patentable subject matter. It must be “useful,” “novel,” and “non-obvious” to a person of ordinary skill in the art. During the patent term, anyone who makes, uses, or sells the patented invention without authority infringes the patent. The remedies for a patent owner in an infringement suit include damages for past patent infringements and an injunction against future infringements.

A. Literal Infringement

In an action for patent infringement, a patentee has the burden of proving infringement by a preponderance of evidence. There are

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The terms of utility and plant patents will be changed to 20 years, measured from the date of filing the application. 59 Federal Register 237 (1994)(to be codified at 37 CFR Parts 1 and 3). The new term will go into effect on June 8, 1995. Id. Current patent terms are measured from the date of patent issuance. The term of design patents remain the same, fourteen years. Id. 35 U.S.C. § 173 (1982).


41. Wegner, supra note 36, at 5.

42. 35 U.S.C. § 101 (1952). Patentable subject matters include “any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof . . .” Id.

The format of a patent mainly consists of: 1) title of the invention, 2) brief summary of the invention, 3) detailed description, and 4) claim or claims. 37 C.F.R. § 1.77 (1983). Only the claim(s) defines the extent and the scope of the invention. 35 U.S.C. § 112 (1975).


44. 35 U.S.C. § 102 (1975). The title of this section is “Conditions for patentability; novelty and loss of right to patent.” Id.

45. 35 U.S.C. § 103 (1984). This section partly reads: “[a] patent may not be obtained . . . if the differences between the subject matter . . . and the prior art are such that the subject matter as a whole would have been obvious at the time of the invention was made to a person having ordinary skill in the art to which the subject matter pertains . . .” Id.


two steps in proving infringement. First, a court construes the patent claims at issue to determine their meaning, or limitations. The claim interpretation is a question of law. Secondly, a fact-finder has to decide “whether each limitation in the properly construed claims is found, either literally or equivalently, in the allegedly infringing” product. If an accused product is found to literally include every element of a claim in a patented invention, a literal infringement has occurred.

However, a defendant can invoke a defense under the reverse doctrine of equivalents if a literal infringement is found. The reverse doctrine of equivalents, which is derived from the famous Graver Tank & Manufacturing Co. v. Linde Air Products Co., states that an accused product may avoid infringement even if it is within the literal words of the claim, if it is “so far changed in principle from a patented article that it performs the same or similar function in a substantially different way.

If an accused product does not include every element of the claim in a patented invention, the accused product can still be found to infringe the patented invention under the doctrine of equivalents if it “performs substantially the same function in substantially the same way to obtain substantially the same result (“function-way-result” test).”

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50. Morton International, 5 F.3d at 1468.
51. Id., (citing Fonar Corp v. Johnson & Johnson, 821 F.2d 627, 631 (Fed. Cir. 1987), cert. denied, 484 U.S. 1027 (1988)).
52. Morton International, 5 F.3d at 1468. The standard of review for a question of law is de novo on appeal. Id.
53. Id.
B. Infringement Under the Doctrine of Equivalents

1. The Famous Graver Tank Case

The doctrine of equivalents is a judicially-developed rule whose origin can be traced back to more than a century ago. The case, Graver Tank & Manufacturing Co. v. Linde Air Products Co., is the most recent case where the U.S. Supreme Court actually applied the doctrine of equivalents and upheld the lower court's finding of infringement. In Graver Tank, the patent at issue was for an electric welding flux. The patent claims for the flux composition included essentially a combination of alkaline earth metal silicate and calcium fluoride. However, the actual formulation of patentee's products contained two alkaline earth metal silicates, and silicates of calcium and magnesium. Defendant's accused product formula substituted silicates of calcium and manganese for silicates of calcium and magnesium.

Because a determination of equivalence is a question of fact, the majority in Graver Tank held that the trial court's finding of infringement under the doctrine of equivalents was not clearly erroneous. The trial court judge found that the accused product formula was "substantially identical in operation and in result" after hearing expert testimony, visiting laboratories, viewing actual demonstrations and various motion pictures of welding operations. The Court emphasized that the doctrine was intended to protect patentees from pirating by potential infringers who design an infringing product around the patented invention while avoiding a literal infringement.

The dissenting justices in Graver Tank criticized the majority for expanding the scope of the patent claims, contrary to the underlying principle of a patent. The dissenting justices noted that the patentee

60. Wegner, supra note 36, at 26-27. In Graver Tank, the Court cited Sanitary Refrigerator Co. v. Winters, 280 U.S. 30 (1929). In Sanitary Refrigerator, the Court found that an accused device had only minor differences from the patented invention and found infringement under the doctrine of equivalents. Id.
62. Id.
63. Id. at 612.
64. Id. at 611.
65. Id. at 608.
66. Graver Tank, 339 U.S. at 614. The dissenting Justices indicated that the holding in White v. Dunbar, 119 U.S. 47, 51 (1886), "forbids treating a patent claim 'like a nose of wax, which may be turned and twisted in any direction, by merely referring to the specification, so as
disclosed silicate manganese in the specification of the patent and failed to include it in the patent claims. An unscrupulous use of the doctrine is "unjust to the public," which is entitled to know the limits and boundaries of the patent claims.

2. Modern Case Law On The Methodology of Analysis Under The Doctrine of Equivalents

In 1982 the Federal Circuit Court of Appeals was established to have exclusive appellate jurisdiction over patent disputes. Since the most recent U.S. Supreme Court decision concerning the doctrine of equivalents dates back to 1950 in Graver Tank, the Federal Circuit Court of Appeals has effectively become the sole authority on any issue arising from the doctrine of equivalents. As such, the Federal Circuit has continued its efforts to refine the methodology of analysis under the doctrine, particularly in light of new and advanced technologies.

In 1987 a divided Federal Circuit Court in Pennwalt Corp. v. Durand-Wayland, Inc., issued an opinion en banc, establishing a standard of analysis for the doctrine. Under the Pennwalt analysis, a court first interprets the patent claims and determines their elements or limitations. Then, a plaintiff is required to show the presence of every element or its substantial equivalent in an accused product in order to prove infringement under the doctrine of equivalents.

In 1990 the three circuit judges in Wilson Sporting Goods Co. v. Dunlop Slazenger Corp. established a method of determining whether prior art restricts the permissible range of equivalents of what to make it include something more than, or something different from what its words express' . . . " Graver Tank, 339 U.S. at 614.

67. Id. at 616. The dissenting Justices suspected that the patentee did not include the silicate manganese in the claims probably due to the fact that the same chemical was similarly used in an expired patent. See Id.

68. Id. at 614.

69. The establishment of the Federal Circuit Court of Appeals was intended to eliminate inconsistent decisions among circuit courts on patent cases. Atlantic Thermoplastics v. Faytex Corp., 974 F.2d 1279, 1281 (Fed. Cir. 1992), (Judge Newman briefly reviewed the history of the Federal Circuit Court of Appeals in its dissenting opinion on the denial of rehearing en banc).

70. See supra note 60 and accompanying text.


72. Id. Seven circuit judges joined the majority opinion, four judges joined the dissent-in-part opinion, one judge filed an additional view and one judge filed a commentary.

73. See Morton International. 5 F.3d at 1468. See supra note 51 and accompanying text.

74. Pennwalt, 833 F.2d at 935 (citing Lemelson v. U.S., 752 F.2d 1538, 1551 (Fed. Cir. 1985)).

is literally claimed in a patent.\textsuperscript{76} \textit{Wilson Sporting Goods} suggests that a court construct a hypothetical claim that is sufficiently broad in scope to literally cover the accused product.\textsuperscript{77} The inquiry then becomes whether the hypothetical claim would have been allowed by the Patent and Trademark Office over the prior art.\textsuperscript{78} If the court finds that the hypothetical claim would not have been allowed, the plaintiff would not be permitted to obtain that coverage of scope under the doctrine of equivalents.\textsuperscript{79} However, in a 1994 decision, three other circuit judges of the same court ruled that the "hypothetical claim" analysis is not mandatory, but an alternative means to the analysis under the doctrine of equivalents.\textsuperscript{80}

3. Two Conflicting Public Policies Underlying The Doctrine

The first policy concern is fair notice to the public.\textsuperscript{81} The public is entitled to know what the metes and bounds of the patent claims are, so that other parties can avoid infringement and design around the patented invention.\textsuperscript{82} The dissenting opinion in \textit{Graver Tank} might have been a representation of the first policy concern.\textsuperscript{83} The second policy concern emphasizes the patent owner’s rights under the patent protection.\textsuperscript{84} The patentee should not be deprived of the benefits of the patent because the competitors appropriate the essence of the patented invention and avoid infringement by simply avoiding the literal languages of the claims.\textsuperscript{85} The majority’s opinion in \textit{Graver Tank} seemingly addressed the second policy concern favorably and stressed the importance of a patent owner’s implicit right under the patent.\textsuperscript{86} A commentator observed that the origin of the doctrine of equivalents is

\textsuperscript{76} \textit{Id.} at 684. "Prior art is the existing body of technical information against which the patentability of an invention is judged." \textit{MANUAL OF PATENT EXAMINING PROCEDURE} (M.P.E.P.) § 2185 (1993).

\textsuperscript{77} \textit{Wilson Sporting Goods}, 904 F.2d at 684.

\textsuperscript{78} \textit{Id.}

\textsuperscript{79} \textit{Id.}

\textsuperscript{80} Conroy v. Reebok International, Ltd., 14 F.3d 1570, 1576 (Fed. Cir. 1994). This is an infringement case involving a patent entitled "Athletic Armor and Inflatable Bag Assembly."

\textsuperscript{81} London v. Carson Pirie Scott & Co., 946 F.2d 1534, 1538 (Fed. Cir. 1991); see Larson, supra note 54, at 28.

\textsuperscript{82} See Larson, supra note 54, at 28.

\textsuperscript{83} See \textit{Graver Tank}, 339 U.S. at 614 (J. Black, dissenting), see also supra note 68 and accompanying text.

\textsuperscript{84} See Larson, supra note 54, at 5, 25-28.


\textsuperscript{86} \textit{Graver Tank}, 339 U.S. at 608. See supra note 65 and accompanying text.
equitable in nature. He suggested that the doctrine only be applied when a patentee can demonstrate an equitable need for its application. A determination of equivalence without consideration of equity will result in uncertain boundaries of the patent protection. Such uncertainty will be likely to discourage competitors from research near the bounds of the protection for the patent.

4. The Defense of Prosecution History Estoppel

An alleged infringer with an accused product is not without defenses against the doctrine of equivalents. The infringer, before or after a finding of equivalence, can invoke a prosecution history estoppel defense. Under the estoppel, a patentee cannot "recapture through equivalence certain coverage [of the patent claims] given up during prosecution." During the prosecution of a patent application, an applicant may have to amend the original application or add certain limitations to narrow the scope of a claim. The amendment often serves to avoid a rejection by a Patent Examiner that the claim was too broad and encompassed prior art. "That is not to say, however, that whenever a limiting amendment or argument is made during prosecution, the patentee loses all coverage between what the claims literally cover and what they would have covered prior to the amendment or argument." Thus, a patentee cannot later in an infringement suit argue that the patent should be interpreted "as if limitations added by amendment were not present."

87. Wegner, supra note 36, at 7-15. The author in Section II of the article traces the origin and the development of the doctrine of equivalents by reviewing earlier cases, one of which dates back to 1813. Id.
88. Id. at 5.
89. Id.
90. Id.
91. Hormone Research Foundation, Inc. v. Genentech, Inc., 904 F.2d 1558, 1564 (Fed. Cir. 1990), quoting Loctite Corp v. Ultraseal Ltd., 781 F.2d 861, 870 (Fed. Cir. 1985). A prosecution history is simply the record of activities of a patent application in the Patent and Trademarks Office, where the Patent Examiner's rejections and objections are recorded and the responses from the applicant are also recorded. See 35 C.F.R. §§ 1.111-1.132 (1994).
92. Hormone Research, 904 F.2d at 1564.
94. Hormone Research, 904 F.2d at 1564.
95. Townsend Engineering Co. v. Hitech Co., Ltd, 829 F. 2d 1086, 1090-1091 (Fed. Cir. 1987). The court reasoned that:

"[h]aving added [claim] limitations to avoid the device disclosed in the prior art, Townsend is barred by prosecution history estoppel from interpreting his claim as broadly as the claim originally filed . . . Townsend is now precluded from contending that the accused device . . . is equivalent to the invention claimed in [Townsend's] patent."

Id. at 1091.
However, any amendment or argument used by the patentee during the prosecution does not automatically estop a patentee from later recapturing the claim coverage given up. The limiting effect of any such amendment or argument, dependent upon their nature and purpose, may have "a spectrum ranging from great to small to zero."  

IV. THE THREE BIOTECHNOLOGY PATENT INFRINGEMENT CASES

The first case, *Hormone Research Foundation v. Genentech*, presents a patent law dilemma where an accused product, which is made by a recombinant DNA method and has a slightly different molecular structure, can potentially infringe a patented product made by a conventional method under the doctrine of equivalents. The second case, *Scripps Clinic Foundation v. Genentech*, presents a similar patent law dilemma where an accused product made by a recombinant DNA method can infringe a patent covering the same product of less purity and potency, which is isolated by a conventional method. The final case, *Wellcome Research Foundation v. Genentech*, illustrates a serious patent law dilemma where the application of the doctrine of equivalents can actually restrain improvements of a patented biological product by a third person who is neither a patent owner nor a licensee.

A. *Hormone Research Foundation v. Genentech, Inc.*

The case presents a patent law dilemma: an accused product can potentially infringe a patented product made by a conventional method under the doctrine of equivalents, even when the accused product has a slightly different molecular structure and is made by a recombinant DNA method. The patent at issue claims human growth hormone (HGH) and its chemical synthetic process known as "Solid Phase Peptide Synthesis." When applying for the patent, the patentee mistakenly believed that the structure of the patented polypeptide (a protein)
was the structure of the naturally occurring HGH. It was later discovered that the amino acid sequence of the patented polypeptide differs from the one of the natural HGH.

Defendant Genentech made the accused product, Protropin, by a recombinant DNA method. The amino acid sequence of Protropin, like the natural HGH, differs slightly from the patented polypeptide at issue. Protropin has an amino acid sequence almost identical to the natural HGH, but with one additional amino acid at the amino end of the sequence. By using recombinant DNA technology, Genentech has been able to produce Protropin (HGH derivative) in marketable quantities for use in the treatments of human growth deficiencies.

In ruling on a motion for summary judgment on the issue of literal infringement, the trial court examined the patent’s specification. The court found that the scope of plaintiff’s patent claims only encompassed chemical substances having the structure identical to the one displayed in the patent claim, which differed from the accused product and the natural HGH. The trial court held that there was no literal infringement of plaintiff’s patented product.

After finding no literal infringement, the trial court proceeded to examine the prosecution history of the patent application. The court found that the patentee surrendered the coverage of natural HGH or HGH derivatives in its claims during the patent application prosecution. During the prosecution, the Examiner rejected some of the proposed patent claims because an article published by Bewley, et al.

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103. Id.
104. Id. at 1560. The patented protein sequence has 190 amino acids while the natural one has 191. Id. The natural HGH has different amino acids in positions 73, 106, and 108. Id.
105. Id. at 1560.
106. Hormone Research, 904 F.2d at 1560.
107. Id.
109. Id. at 1100-1102.
110. Hormone Research, 904 F.2d at 1563-1564. In the patent application, the applicant specifically exhibited a structure of a polypeptide that was previously thought as the correct one of the natural HGH and the structure of the later patented one (which also turned out to be incorrect after the patent was issued). Id. at 1563. The patentee explained in the specification that there were similarities between the two structures and the differences in the number and sequence of amino acid residues. Id.
111. 708 F. Supp. at 1102.
112. Id. at 1103-1106.
disclosed carbaminomethylated reduced HGH. The patentee, in his two written responses to the Examiner’s rejections, stated as follows: “Claims . . . are specific to the structure[s] [displayed] . . . The claims are therefore limited to the structures shown in the drawings and are not directed broadly to HGH or its derivatives. No such structure is disclosed in the reference [the cited article] . . .” The trial court granted a motion for partial summary judgment filed by Genentech, holding that the prosecution history estopped the patentee from invoking the doctrine of equivalents to include the naturally occurring HGH.

On appeal, Federal Circuit upheld the trial court’s ruling finding no literal infringement by the accused product, although the trial court applied an improper methodology in its reasoning. However, the appellate court reversed the trial court’s holding in which the prosecution history precluded the application of the doctrine of equivalents. The court held that summary judgment on the application of the doctrine of equivalents under the circumstances was improper because there were genuine issues of material fact as to the circumstances surrounding the communications between the Examiner and the patentee. The appellate court noted that there might be several possible explanations for patentee’s statements to the Examiner during the prosecution, and the patentee was entitled to introduce extrinsic evidence to explain the statements in a trial. The appellate court remanded the case for a factual determination of the intent and the

113. Hormone Research, 904 F.2d at 1565. 35 U.S.C. § 102 (b)(1982) reads: “[a] person shall be entitled to a patent unless, . . . (b) the invention was . . . described in a printed publication . . . more than one year prior to the date of the application for patent in the United States.”
114. 708 F. Supp. at 1104 (emphasis added).
115. 708 F. Supp. at 1102-1106. This is the First Motion for Partial Summary Judgment filed by Genentech to determine that defendants do not infringe certain claims in the patent at issue. Id. at 1100.
116. 904 F.2d at 1563. The trial judge interpreted the term, “corresponding,” by using a dictionary to determine what the patentee meant, when he used the term in the claims to refer to the structure of the patented product. Id. The appellate court found that the use of dictionary here was improper because a patentee may be his or her own lexicographer in a patent application and thus “may use terms in a manner contrary to or inconsistent with one or more of their ordinary meanings.” Id.
117. Id. at 1566-1567.
118. Id. at 1566.
119. Id. at 1566-1567. One of the possible interpretations is that the patentee might mean that he surrendered only the carbaminomethylated substitutes derived from the natural HGH. Id. at 1566. Another plausible explanation of the patentee’s statement or argument during the prosecution is that the cited article did not disclose the structure of the natural HGH or teach how to make the natural HGH. Id. at 1566-1567. The patentee may argue that the cited article can not be used as prior art under 35 U.S.C. § 102 (b). See id. at 1566.
effects of the patentee's statements made before the Examiner. The court instructed the trial court to determine whether Genentech's accused product is within a "legally permissible range of equivalents" if the court later finds that prosecution history estoppel does not apply.

However, the appellate court did not review the trial court's denial of defendant's second motion for partial summary judgment. In this motion, the defendant attempted to seek a ruling that defendant's recombinant DNA method of making the accused product does not infringe upon patentee's claimed Solid Phase Peptide Synthesis method of synthesizing the patented product. In its reasoning, the trial court observed that the patentee did not specify in the claims what method would be applied. Rather, the Solid Phase Peptide Synthesis method was not claimed but only disclosed in the specification as the patentee's "preferred embodiment of the invention." The trial court denied defendant's motion, holding that the claims, rather than the specification, measure the scope of the patented invention. Thus, the case presents a patent law dilemma. A finding of infringement by Protropin under the doctrine of equivalents can prevent

120. Id. at 1567.
121. 904 F.2d at 1566 n. 14. The appellate court also vacated the summary judgment holding that some patent claims were not enabling because there was a genuine issue of material fact. Id. In other words, a person with a reasonable skill in the art would not have been able to synthesize the chemical in accordance with the teaching in the patent specification. 35 U.S.C. § 112 (1975). The court observed that the trial court's decision on this issue might have been influenced by the new and advanced recombinant DNA technology method in producing the HGH. 904 F.2d at 1568.
122. The defendant probably did not appeal the trial court's denial of the second motion for partial summary judgment.
123. 708 F. Supp. at 1105-1106. Claim 1 of the patent claims a "method of producing synthetic human pituitary growth hormone which comprises" three general steps, the first of which involves forming an amino acid chain "in the sequence of natural human pituitary growth hormone." Id. at 1098 (citing the patent Claim 1). "Claim 3 claims a method of producing a substance having growth-promoting activity which comprises the same three steps except the first step requires that the chain be formed in a sequence corresponding to Fig. 2 (the patented structure) . . . of the accompanying drawing." Id. at 1099.
125. Id. There may be several ways to carry out an invention. However, 35 U.S.C. § 112 requires that an inventor in the patent specification only sets forth the best mode of carrying out the invention in full, clear, concise and exact terms. 35 U.S.C. § 112 (emphasis added).
126. 708 F. Supp. 1096, 1107 (N.D.Cal.1988) (citing Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 699 (Fed. Cir. 1983)). The trial court also denied plaintiff's cross-motion on this issue. Id.
Genentech from using, selling, and making recombinant Protropin. Ironically, the development and production of the recombinant HGH derivative are very crucial to making marketable quantities for use in the treatment of growth deficiencies in humans.

B. *Scripps Clinic & Research Foundation v. Genentech, Inc.*

The case illustrates certain restraining effects of the patent law upon the application of recombinant DNA technology. Plaintiff Scripps owns patents which describe and claim highly purified and concentrated human or porcine Factor VIII:C, a protein, which is isolated by an immunological and biochemical method. Scripps patents also claim the process of isolation and purification of Factor VIII:C from human and porcine plasma. However, defendant Genentech was the first party who isolated the gene for Factor VIII:C and identified the DNA sequence of the gene. After more than three years of research efforts, Genentech developed a recombinant DNA method to produce Factor VIII:C in baby hamster kidney cells.

Factor VIII:C is present in the bloodstream and plays an essential part in blood clotting and wound healing. One of the disadvantages

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127. 666 F. Supp. 1379.
128. 666 F. Supp. at 1383-1385. Factor VIII:C in the bloodstream attaches to another similar protein, Factor VIII:RP. *Id.* Under the Scripps patent, Factor VIII:C is obtained by pouring large quantities of human or porcine blood plasma over monoclonal antibodies specific to Factor VIII:RP. *Id.* Such monoclonal antibodies have been attached to a solid phase, such as small beads. *Id.* Almost all substances will pass through the solid phase while the Factor VIII:C-Factor VIII:RP complex is attached to the solid phase. *Id.* Then, the Factor VIII:C is eluted from the solid phase, being harvested and concentrated. *Id.*

The Factor VIII:C claimed is from either human or porcine human blood. *Id.* at 1383.

129. *Id.*
130. 666 F. Supp. at 1383-1384.
131. *Id.* The gene (DNA) fragment of Factor VIII:C is inserted into a plasmid, a circular DNA molecule that replicates itself in cells. The recombined plasmid is then introduced into a baby hamster kidney cell, which will replicate indefinitely. The hamster cells with the Factor VIII:C gene will produce the protein, Factor VIII:C. The Factor VIII:C will then be isolated from the hamster's cells. *Id.* See supra note 28 and accompanying text.


132. 666 F. Supp. at 1382-1383. The blood clotting process, though not fully understood, may be generally described as follows:

The clotting process begins when platelets in the bloodstream adhere to the site of a wound. The platelets would be dislodged, however, unless bound in place by strands of fibrin, an insoluble polymer. The formation of a network of fibrin from its soluble precursor, fibrinogen, is critical to clotting. That formation is the result of a complex series of interactions between blood proteins. Factor VIII:C is one of the agents that activate other proteins essential to this process. A deficiency in
of Scripps patented method is that large quantities of blood either from humans or pigs are needed. Likewise, the Factor VIII:C, isolated according to Scripps’ method, may potentially carry infectious agents from the blood donors. However, Genentech’s utilization of recombinant DNA technology in making Factor VIII:C offers certain advantages. The production of the Factor VIII:C by Genentech’s method eliminates the need for a large pool of donor’s blood and the potential risk of transmitting infectious agents from plasma donors to the recipients.

Scripps mainly claimed its invention under two types of claims, 1) product-by-process claims, and 2) product claims. During summary judgment, two of the issues before the trial court were: 1) what is the scope of Scripps’ patents, and 2) whether Factor VIII:C made by recombinant DNA technology falls within the scope, hence, whether they infringe?

In ruling for a motion for partial summary judgment, the trial court held that a “product-by-process claim” is only infringed by an accused product made by the same process. The trial court found that Factor VIII:C produced by the recombinant DNA process did not infringe Scripps Factor VIII:C claimed in the product-by-process claims because the accused Factor was produced by an entirely different process. However, in its early research of human Factor VIII:C and the identification of its amino acid sequence, Genentech used the Factor VIII:C produced by Dr. Tuddenham in England who utilized the same method as claimed in Scripps product-by-process claims. As a result, the trial court found that Genentech literally infringed the

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Factor VIII:C, therefore, prevents blood clotting. A person lacking this Factor will be exposed to a risk of hemorrhaging from even a minor wound.

Id. at 1383.

Id. at 1384.

Id.

666 F. Supp. at 1386. A product of invention may be defined by the process of making it if the English language is inadequate to describe the invention. Id. “However, the invention so defined is a product, not a process.” Id., citing In re Bridgeford, 357 F.2d 679, 682 (C.C.P.A. 1966).

For example, Claim 13 of the patent claims: “Highly purified and concentrated human or porcine VIII:C prepared in accordance with the method of claim 1.” 666 F. Supp. at 1385.

Id. at 1389. For example, Claim 24 of the patent claims: “A human VIII:C preparation having a potency in the range of 134 to 1172 units per ml and being substantially free of Factor VIII:RP.” Id. at 1385. “Potency” refers to the amount of activity in a given volume of solution. Hormone Research, 927 F.2d at 1569 n. 4. (Fed. Cir. 1991).

666 F. Supp. at 1386-1387. The trial court cited a U.S. Supreme Court decision in 1884 and other Circuit Courts’ decisions. Id.

Id. at 1388.

Id. at 1387.
product-by-process claim by using the product given by Dr. Tud- 
denham.\textsuperscript{141} The court held that the plaintiff was not entitled to an 
“equitable” ruling on the doctrine of equivalents because a literal in-
fringement had been found.\textsuperscript{142}

With respect to the “product claims” in the Scripps patent, the 
court found that the accused recombinant Factor VIII:C infringed the 
Scripps product claims, because the accused Factor VIII:C is the same 
as the human Factor VIII:C, regardless whether Factor VIII:C is di-
rectly isolated from the plasma or is made from recombinant baby 
hamster cells.\textsuperscript{143}

On appeal, the Federal Circuit Court reversed the trial court’s 
ruling that the Factor VIII:C produced by the recombinant DNA 
method infringed the product claims of Scripps’ patent as a matter of 
law.\textsuperscript{144} The appellate court noted that there were genuine issues of 
material fact as to the purity and potency of the accused product in 
comparison with Scripps’ product claims.\textsuperscript{145} The court added that 
Genentech might be entitled to use the reverse doctrine of equivalents 
as a defense.\textsuperscript{146}

The Federal Circuit Court also reversed the trial court’s ruling 
that Scripps’ product-by-process claim was not infringed by 
Genentech’s product made by the recombinant DNA method.\textsuperscript{147} The appellate court held that the coverage of the product-by-process claim 
was not limited to the product prepared by the process set forth in the 
claims.\textsuperscript{148}

However, one year later after the Scripps decision, a panel of 
judges for the Federal Circuit in \textit{Atlantic Thermoplastic Co. Inc. v. 
Faytex Corp.}\textsuperscript{149} rejected the Scripps holding on the issue of product-

\textsuperscript{141} Id. at 1387-1388.
\textsuperscript{142} Id. at 1389.
\textsuperscript{143} Id. at 1391.
\textsuperscript{144} 927 F.2d at 1581.
\textsuperscript{145} Id. The patented Factor VIII:C in the patent is partly defined by its purity and its 
potency (biological activity) in the product claims, as opposed to the product-by-process claims 
where the product is defined by a process resulting in the product. \textit{See supra} notes 136-137.
\textsuperscript{146} Id. at 1581. The court stated that the reverse doctrine of equivalent was derived from 
text.
\textsuperscript{147} 927 F.2d at 1583.
\textsuperscript{148} Id.
\textsuperscript{149} 970 F.2d 834 (Fed. Cir. 1992) (holding on the issue of infringement of product-by-
process claims); 974 F.2d 1279 (Fed. Cir. 1992), (dissenting opinions to the denial of rehearing 
\textit{en banc}); 974 F.2d 1299 (Fed. Cir. 1992) (Judge Rader’s opinion concurring the denial of rehear-
ing \textit{en banc}); 5 F.3d 1477 (Fed. Cir. 1993) (remanded on issue of on sale bar).
by-process claims.\textsuperscript{150} The \textit{Atlantic Thermoplastic} panel held that an accused product infringes a product-by-process claim only if the accused product is made by the same process set forth in the claim.\textsuperscript{151} More importantly, the Federal Circuit twice refused to grant a rehearing \textit{en banc} to reconsider the prior ruling by the \textit{Atlantic Thermoplastic} panel on the issue of product-by-process claims.\textsuperscript{152}

The \textit{Scripps} decision manifest another patent law dilemma: a finding of literal infringement against Genentech will surely preclude Genentech from making the recombinant Factor VIII:C, which has a better quality and potency for use in more effective and safer treatments of hemophilia patients. Likewise, a finding of infringement will be unjust to Genentech because it was the first party whose efforts led to the isolation of the gene for Factor VIII:C and the identification of the DNA sequence of the gene.

C. \textit{Genentech, Inc. v. Wellcome Foundation, Ltd.}\textsuperscript{153}

The case illustrates a serious patent law dilemma where the application of the doctrine of equivalents can potentially restrain improvements of a patented biological product by a third person who is neither a patent owner nor a licensee. The recent appellate court decision in \textit{Wellcome} may actually have resolved such dilemmas and placed a heavier burden on plaintiffs to prove infringement under the doctrine of equivalents in defendants' favor.

1. Background

This is a patent infringement case involving three patents (the '603, '075, and the '330 patents) that describe and claim a protein, called tissue plasminogen activator ("t-PA"), and its production process.\textsuperscript{154} Genentech, one of the plaintiffs, owns an exclusive license to the '603 patent which claims human t-PA isolated and purified from certain human cancer cells.\textsuperscript{155} Genentech is the owner of the '075 and '330 patents at issue. The '075 patent claims a DNA isolate contain-
ing human t-PA, a recombinant vector containing human t-PA DNA sequence, and a cell culture capable of producing human t-PA through the use of recombinant DNA technology. The '330 patent claims the process of producing human t-PA by recombinant DNA technology.\textsuperscript{156}

Human t-PA is actually an enzyme which plays a very important physiological role within the human body. Its main function is to cut plasminogen, an inactive enzyme present in the blood, into plasmin (active enzyme). Plasmin in turn breaks down fibrin filaments in a fibrin network (a clot).\textsuperscript{157} Incidentally, more than ninety percent of heart attacks in humans are caused by clots in the vessels that supply blood to the heart muscles.\textsuperscript{158} It has been found that administration of certain dosage of t-PA to a heart-attack patient accelerates the clot dissolving process, stops the heart attack, and minimizes damages to the patient’s body.\textsuperscript{159}

The protein, t-PA, is composed of 527 amino acids in length. The stretch of the 527 amino acid sequence is commonly divided into five regions, called domains, referred to as (1) an “F” domain, (2) an “E” domain, (3) a Kringle 1 [“K1”] domain, (4) a Kringle 2 [“K2”] domain, and (5) a “serine protease” domain.\textsuperscript{160} The F domain allows t-PA to bind to fibrin, while the K1, K2, and serine protease regions are the enzymatically active portions of the t-PA, which cleave the plasminogen present in the bloodstream.\textsuperscript{161}

The two accused products at issue are met-t-PA and FE1X proteins. Defendants Wellcome Foundation (Wellcome) produced met-t-PA which contains almost an identical sequence to that of human t-PA, except for one amino acid substitution.\textsuperscript{162} It is contended that the substitution causes the met-t-PA molecule to have a different secondary and tertiary folding structure, which may weaken its binding affinity to fibrin.\textsuperscript{163} In clinical trials, met-t-PA has been proven to be

\textsuperscript{156} Id.
\textsuperscript{157} 14 U.S.P.Q.2d 1363, 1365. Human t-PA is activated by a final product of the cascade reactions that initially formed the blood clot. Id. The formation of a clot is a physiological mechanism in the human body to block broken blood vessels before the vessels are repaired. Once the broken vessel has been repaired, the clot is no longer needed.
\textsuperscript{158} Id.
\textsuperscript{159} Id. A heart attack is mostly caused by blood clots formed in the arteries that directly supply blood to the heart muscle. Id. The blocking of the vessels by the clots stops the circulation of blood through the affected blood vessels. Id. Failure to dissolve the clots in a timely manner will result in heart muscle damage or death. Id.
\textsuperscript{160} 14 U.S.P.Q. 2d at 1365.
\textsuperscript{161} Id.
\textsuperscript{162} Id. at 1368. The substitution is at position 245, replacing valine by methionine. Id.
\textsuperscript{163} Id. at 1370-1371.
associated with a lower rate of serious, life-threatening, or fatal bleeding incidents as compared with Genentech's recombinant human t-PA. Another named defendant, Genetics Institute (Genetics), manufactured FEIX which has a deletion of eighty-one amino acids (the entire "F domain") from human t-PA and an amino acid substitution at the same position as that of met-t-PA. FEIX proteins have a forty-two minute clearance rate in the bloodstream as compared to four minutes of human t-PA's. Likewise, FEIX is reportedly associated with less risk of uncontrolled bleeding as compared to human t-PA.

2. Summary Judgment

The summary judgment only involved the '603 and '075 patents. The trial court first generally defined that the patent coverage for human t-PA in both the '603 and '075 patents includes three elements of limitation: 1) it must be a human t-PA or a naturally occurring variant, 2) it must be immunologically distinct from urokinase, and 3) it must have a specific activity of about 500,000 IU/mg or about 90,000 IU/mg. However, the Genentech '075 patent did not define "human t-PA" produced from recombinant DNA technology by specific activity of 500,000 IU/mg, as did the human t-PA in the '603 patent claim. Because the plaintiffs were unable to demonstrate that the accused products (met-t-PA and FEIX) were naturally present in the human body, the court found no literal infringement by the two accused substances.

Thereafter, the trial court applied the three-prong test (function-way-result) in its infringement analysis under the doctrine of equivalents. First, the court generally observed that the human t-PA in the '603 and '075 patents stimulates the dissolution of fibrin clots by way of enzymatic cleavage of plasminogen to plasmin. Finding that both of the accused products stimulate the dissolution of fibrin

164. Id. at 1371.
165. 14 U.S.P.Q. 2d at 1369.
166. Id. A longer clearance rate of a chemical in the blood means that the chemical will stay in the blood for a longer time before it is eliminated from the blood stream, hence the decrease in the number of continuous infusion of a t-PA derivative to a patient. Id.
167. 29 F.3d at 1569 n. 43.
168. Three substances are able to convert inactive plasminogen into active plasmin; they are streptokinase, urokinase, and t-PA. Streptokinase is made by bacteria and urokinase and t-PA are naturally present in the human body. 14 U.S.P.Q.2d 1363, 1365. Only the protein, t-PA, is relevant to the case. Id.
170. 29 F.3d at 1561-1562. Neither did they so define "human t-PA" in the '330 patent. Id.
171. 14 U.S.P.Q. 2d at 1369-1370.
172. 14 U.S.P.Q. 2d at 1370.
clots by a way of enzymatic cleavage in the fibrin, the court concluded
that the two accused products have substantially the same "function"
and achieve substantially the same "result." However, defendants
vigorously contended that the altered structures of the two accused
products behave differently than human t-PA does. In light of the
altered structures in the two accused products and the different behav-
ior for FEIX, the trial court held that there were genuine issues of
material fact as to whether the two accused products employ substan-
tially the same "way", namely, enzymatic cleavage, to fulfill their
functions and achieve the result. The issues were for the trier of
fact to decide.

3. Trial Court's Final Decision

After the trial, the jury rendered a verdict finding that the two
accused products infringed all three patents at issue under the doctrine
of equivalents. The trial court upheld the jury's decision, finding
that there was substantial evidence to support the jury finding that the
two accused products met the three-prong test. However, the trial
court did not elaborate extensively on the evidence in its opinion.
With respect to met-t-PA, the court noted that the sole difference be-
tween met-t-PA and human t-PA is the amino acid substitution which
is a result of "an inadvertent cloning error by Wellcome in its effort to
copy human t-PA." Likewise, the trial court agreed with the jury’s
finding in that FEIX comprises all three elements of limitation as the
human t-PA in the '603 patent, including the specific activity of
"about 500,000 IU/mg." The trial court indicated that the patents at
issue claim all human t-PA derivatives which retain the essential Krin-
gle and serine protease regions. The variation of amino acids in those
two regions, as in met-t-PA and FEIX, is not relevant, but the reten-
tion of the two regions as a whole is relevant.

Both defendants filed appeals thereafter. However, Wellcome
voluntarily dismissed its appeal with prejudice and announced its in-
tention to discontinue developing a t-PA product. Plaintiffs imme-

173. Id.
174. Id. at 1370-1371.
175. Id.
176. Id. at 1371.
177. 798 F. Supp. at 213.
178. Id. at 215-216.
179. Id. at 215.
180. Id. at 216.
181. Id. at 216.
182. 29 F.3d at 1560.
diately filed a motion for permanent injunction against Wellcome, which the trial court granted.\textsuperscript{183}

4. The Federal Circuit Court of Appeals’ Decision

In 1994, two years after the trial court decision, the Federal Circuit Court of Appeals ruled on Genetics’s appeal, reversing the trial court’s decision and finding that the jury’s verdict was not supported by substantial evidence.\textsuperscript{184} The Court of Appeals held that the FE1X product does not infringe human t-PA claimed in the ‘603, ‘075, and ‘330 patents under the doctrine of equivalents.\textsuperscript{185} In its ruling, the Court of Appeals first determined three threshold questions related to claim interpretation and held as follows:\textsuperscript{186} (1) the specific activity limitation, 500,000 IU/mg, for human t-PA in the ‘603 patent claim is not implicit in the ‘075 and ‘330 patent claims;\textsuperscript{187} (2) the 500,000 figure in the ‘603 patent is IU/mg, a unit measured by using a bovine fibrin plate assay;\textsuperscript{188} and (3) the literal meaning of “human t-PA” in the ‘075 and ‘330 patent claims refers to a narrow structural definition, \textit{e.g.}, “human t-PA produced through recombinant DNA technology but having the same structure as natural t-PA.”\textsuperscript{189} The court found at least four possible definitions for “human t-PA” in the ‘075 and ‘330 patent specifications, their prosecution history, and prior art.\textsuperscript{190} The court indicated that the diverse definitions in Genentech’s

\textsuperscript{183.} 798 F. Supp. at 213.
\textsuperscript{184.} 29 F.3d 1555.
\textsuperscript{185.} Id. at 1567, 1569. However, the met-t-PA product was not at issue on appeal because Wellcome, which made the met-t-PA product, voluntarily dismissed its appeal with prejudice. \textit{Id.}
\textsuperscript{186.} Claim interpretation is a question of law and the standard of review is \textit{de novo} on appeal. \textit{Morton International}, 5 F.3d at 1468.
\textsuperscript{187.} 29 F.3d at 1561-1562. Human t-PA in the ‘603 patent claim is directly isolated from human cells while “human t-PA” in the ‘075 and ‘330 patents are produced by recombinant DNA technology. The ‘075 and ‘330 patent claims did not define human t-PA by its specific activity measured by the bovine fibrin plate assay. \textit{Id.}
\textsuperscript{188.} \textit{Id.} at 1562-1563. The court indicated that the figure must be assigned to a specific assay type in order to distinguish the prior art value of similar product, 266,000 IU/mg. \textit{Id.}
Expert testimonies indicated that different assay types yield different figures for the same substance. \textit{Id.} at 1566.
\textsuperscript{189.} \textit{Id.} at 1562-1563.
\textsuperscript{190.} \textit{Id.} The first definition is adopted by the appellate court. The second definition is a broader structural one, \textit{e.g.}, “all products containing the ‘essential’ Kringle region, and the Serine Protease region.” \textit{Id.} The third possible definition has an even broader scope, \textit{e.g.}, “all products containing just the enzymatically active portion, the Serine Protease portion.” \textit{Id.} at 1563-1564. The fourth possible definition is a functional one, \textit{e.g.}, products “capable of catalyzing the con-
two patents are either "a conscious attempt to create ambiguity about the scope of the claims, or a desire" to claim a scope that is not warranted by the specifications on the part of Genentech.\textsuperscript{191}

With respect to the issue of infringement upon the '603 patent, the court noted that the only probative testimony during the trial indicated that FEIX has an activity between 208,116 to 299,484 IU/mg measured by the bovine fibrin plate assay.\textsuperscript{192} The FEIX activity thus fell outside the permissible range of equivalent value for the '603 patent, \textit{i.e.}, about 500,000 IU/mg.\textsuperscript{193}

In the process of reviewing the infringement upon '705 and '330 patents, the Court of Appeals seemingly placed a specific, perhaps heavier, burden upon the plaintiffs in meeting the three-prong test under the doctrine of equivalents. The court required the evidence be "sufficiently particularized" to meet the three-prong test.\textsuperscript{194} First, the court determined the "operative definition" of human t-PA for the purpose of equivalency analysis.\textsuperscript{195} After looking at the intended function of the patented product "in the context of the patent, the prosecution history, and the prior art,\textsuperscript{196} the court concluded that fibrin binding during the clot-dissolving process is a critical component of human t-PA "function."\textsuperscript{197} The operative definition of human t-PA should have been "catalyzing the conversion of plasminogen to plasmin and binding to fibrin."\textsuperscript{198} Expert testimonies indicated that the fibrin binding is likewise critical to the therapeutic effects of human t-PA.\textsuperscript{199} The court found that the plaintiffs failed to present "particularized evidence" to show that FEIX functions in substantially the same "way" as human t-PA or achieved substantially the same "results".\textsuperscript{200}

Rather, the evidence from the record pointed to the contrary. First, the FEIX fibrin binding affinity is only 40 percent of that of

\begin{footnotesize}
\begin{itemize}
\item[\textsuperscript{191}] Id. at 1564. Among the four definitions, the first one is more consistent with the practice of the U.S. Patent and Trademark Office. \textit{Id.}
\item[\textsuperscript{192}] Id. at 1565-1566.
\item[\textsuperscript{193}] 29 F.3d at 1566-1567.
\item[\textsuperscript{194}] \textit{Id.} at 1567 \textit{(citing Graver Tank v. Linde Air Products, 339 U.S. at 608.)}
\item[\textsuperscript{195}] 29 F.3d at 1567.
\item[\textsuperscript{196}] \textit{Id.}
\item[\textsuperscript{197}] \textit{Id.} The fibrin binding is essential to reduce the risk of hemorrhaging which is caused by lack of blood clotting around a wound in the blood vessels. \textit{See id.} Likewise, the fibrin binding is an important distinction between t-PA and two other different plasminogen activators, urokinase and streptokinase. \textit{Id. See also supra} note 112.
\item[\textsuperscript{198}] \textit{Id.}
\item[\textsuperscript{199}] 29 F.3d at 1568-1569.
\item[\textsuperscript{200}] \textit{Id.} at 1568. The court found that the expert testimonies about FEIX fibrin binding were speculative, tentative, and conclusive.
\end{itemize}
\end{footnotesize}
human t-PA as a result of the deletion of the eighty-one amino acids including the entire F domain, despite the fact that fibrin-binding is crucial to the therapeutic effects of human t-PA.\textsuperscript{201} Secondly, the substitution of an amino acid in the FE1X amino acid sequence increases the binding affinity of FE1X, which sufficiently renders it therapeutically effective, in spite of the fact that the F domain is deleted from FE1X.\textsuperscript{202} Thus, the “way” of FE1X binding is not substantially the same as human t-PA.\textsuperscript{203} Finally, the increase of the FE1X clearance rate by ten times in the human body, as compared to human t-PA, is certainly a definite indication of different and enhanced “result” achieved by FE1X.\textsuperscript{204} The court indicated that the mere showing of the K2 region’s role in binding for both t-PA and FE1X was not sufficient to show a substantially identical “way” to achieve substantially the same “result,” when the property and structure of FE1X have profound differences.\textsuperscript{205} Likewise, FE1X’s decreased binding affinity to endothelial cells, which reduces the risk of uncontrolled bleeding, is another indicator of a different “result”.\textsuperscript{206}

Thus, the trial court’s ruling in \textit{Wellcome} presents a patent law dilemma where a better therapeutic product can be found infringing a less-effective patented product and be prevented from entering the market. The Federal Circuit Court of Appeals effectively relieves FE1X from a possible injunction and makes it available to the public use for the treatment of heart-attack patients. The appellate court’s narrow interpretations of the three-prong test may actually, at least partly, resolve the dilemma between the doctrine of equivalents and biotechnology.

V. RESOLVING THE DILEMMAS BETWEEN THE PATENT LAW AND BIOTECHNOLOGY

A. The Dilemmas

The three biotechnology patent infringement cases discussed above illustrate the existence of a certain degree of friction between biotechnology and the intended purposes of patent law. Likewise, the application of the doctrine of equivalents generates invisible tensions between the patent owners and the public. The tensions are mani-

\textsuperscript{201} Id. at 1568-1569.

\textsuperscript{202} Id. The F domain allows t-PA to bind to fibrin. \textit{Supra} note 160 and accompanying text.

\textsuperscript{203} Id.

\textsuperscript{204} Id.

\textsuperscript{205} Id.

\textsuperscript{206} Id. at 1569. Endothelial cells make up the lining of the blood vessels. Id. at 1569, n.43.
fested in the two conflicting public policies: protecting patent owners’ rights to their invention on the whole versus the public’s entitlement to know the limits of the patent claims.207

In Hormone Research, the chemical structure of the patented product differs from both the structures of natural HGH and the accused recombinant product, Protropin. Furthermore, Protropin was made by the recombinant DNA method as compared with the conventional method claimed in the patent. Yet on remand, Protropin can potentially be found to infringe the patented product. A finding of infringement is likely to deter a third party who is neither a patent owner nor a licensee from developing a recombinant DNA method for the production of a product like Protropin, which presumably has better quality than the patented one. Likewise, an infringement ruling will definitely prevent Protropin from reaching the consumers, or the patients with growth deficiencies, to the public’s detriment.

In Scripps, a similar dilemma to the one in Hormone Research exits. The accused Factor VIII:C is produced by recombinant DNA technology while the patented Factor VIII:C is isolated by a conventional means from the plasma. Although the chemical structure of the accused Factor VIII:C is identical to the one of the patented Factor VIII:C, the accused Factor VIII:C probably has better purity and potency than those of the patented Factor VIII:C because of the advantages of recombinant DNA technology. In addition, recombinant DNA technology enables companies to make a product in marketable quantities. An adverse ruling against the defendant will certainly preclude recombinant Factor VIII:C from entering the market, and greatly restrict the application of recombinant DNA technology.

In Wellcome, the trial court’s decision in 1992 was likely to concern the biotechnology industry, conceivably, as well as the fields related to medicine. The decision would have prevented the defendants from making, using, and selling FEIX which is a better therapeutic product than the patented human t-PA, not considering the waste of human efforts and monetary investments the defendants put into research and development of FEIX.208 Likewise, a better t-PA product means better and more effective treatments to heart-attack patients, as in the case of FEIX. The application of the doctrine of equivalents apparently exerts restraining effects upon the improvement of a patented biological product to the society’s detriment.

207. Supra notes 81 and 84, and accompanying text.

208. 29 F.3d at 1569. Genetics defendants expended $20 million and 130 man-years to develop FEIX. Id. at 1564, n. 24.
In fact, defendant Wellcome voluntarily dismissed its appeal with prejudice on the issue of infringement by its product, met-t-PA. The plaintiffs immediately filed a motion for a permanent injunction against Wellcome, which the trial court granted.

Thus, the potential and actual outcomes of these cases manifest the legal dilemmas in that the patent law, particularly the doctrine of equivalents, can actually restrain the advancement of biotechnology to the public’s detriment. The outcomes apparently contradict the underlying purposes of the patent law, e.g., to promote and advance technologies.

B. The Implications From The Recent Wellcome Decision

The recent 1994 Wellcome decision by the Federal Circuit Court of Appeals will be likely to have great impacts on the biotechnology industry. It will surely dismiss some of the concerns surrounding the biotechnology industry, as well as the application of doctrine of equivalents. First, a markedly improved therapeutic product with structural alterations may be able to survive an infringement attack, particularly under the doctrine of equivalents. Arguably, the Court of Appeals may have placed a more specific, perhaps heavier, burden upon the plaintiffs to satisfy the three-prong test. The court requires that “particularized” evidence be presented to support findings under the three-prong test.209

Secondly, the appellate court disagreed with trial court’s broad and generalized definitions of the terms, “function and result”, when defining human t-PA for the purpose of equivalency analysis. In its ruling, the appellate court specifically defined and narrowed the scopes of those terms. With respect to the “function” of human t-PA in two of the three patents at issue, the court included a critical biochemical property of the t-PA molecule, e.g., fibrin binding.210

Thus, in future biotechnology patent infringement cases, plaintiffs may have to prepare to rebut any narrower interpretation of “function” for their patented products, in order to successfully invoke the doctrine of equivalents. Thirdly, the plaintiffs will probably have a heavier burden to prove that an accused product behaves in substantially the same “way”, whenever the accused product manifests a markedly improved property with an altered molecular structure.211 The plaintiffs may have to present some “particularized” evidence to show how the accused product interacts with others at the molecular

209. Id. at 1567 (citing Graver Tank v. Linde Air Products, 339 U.S. 605, 608.)
210. Id. at 1567-1568.
211. Id. at 1569.
Finally, the appellate court seemingly narrowed the scope of the t-PA “result” in the analysis under the three-prong test. In the lower court, the “result” of t-PA and FE1X was broadly defined as “dissolution of fibrin clots.” However, the appellate court included other factors in the scope of FE1X “result”, such as the FE1X clearance rate in the human body and its affinity for binding to endothelial cells. It is apparent that the effectiveness and the safety of the therapeutic products at issue become some of the elements of their “result” under the three-prong test, in addition to the generalized “result” of dissolving clots.

C. Suggested Resolutions Of The Dilemmas By Commentators

A commentator noted that the doctrine of equivalents was strictly based upon equitable principles before 1850. Any equity-free determination of equivalence will discourage competitors from doing research around the boundary of the scope of patent claims. It is suggested that a plaintiff show an equitable need for the application of the doctrine and an equitable analysis should be needed after a finding of equivalence under the “function-way-result” test. The commentator observed that Hormone Research would have been an appropriate case to apply the equitable analysis. Although an equivalent was found, this was not a case where the accused infringer was attempting to copy the “patented product”. Rather, the accused infringer was making efforts to copy a “natural product” by using recombinant DNA technology. An infringement should not have been found under the equitable consideration.

Analogizing to a division of patent classification, the plant patents, another commentator suggested that Congress classify the bio-

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212. 29 F.3d at 1569. The court did not specify what type of scientific evidence of sufficient details would meet the proof of “particularized evidence,” even though the court indicated that a requirement of proof of specific causes for the enhanced properties may be improper when the field of science has not had clear understanding of the causes. Id. See also id. at n. 45.
213. Id. at 1568-1569.
214. 14 U.S.P.Q. 2d. at 1368.
215. 29 F.3d at 1567-1569.
216. Id.
218. Id.
219. Id. at 5, 42.
221. Id. at 33.
222. Id.
223. Id.
technology patents into an entirely different scheme of intellectual property protection. This commentator opined that one should not force either the biotechnology patents or certain patent doctrines to fit into each other by making compromising modifications.

One commentator suggested that legislative intervention may be needed to resolve the apparent dilemma between the patent law and the rapidly developing biotechnology industries. One of the means to resolve the dilemma is to promulgate rules stating that the scope of a product made or isolated from a traditional way will not encompass the same product made by recombinant DNA technology.

This writer observes that the suggested introduction of equitable consideration into the analysis under the doctrine of equivalents may not be feasible, because a standard for an equitable consideration may be too broad and vague. As a result, more ambiguity and uncertainty will be injected into the already-muddy area of analysis under the doctrine of equivalents. While the legislative intervention may be feasible, this writer notes that it may not be wise to seek legislative intervention and create an exception to a fairly-settled field of patent law, whenever there is friction between the “old” law and a new technology.

In comparison with the history of biotechnology, the doctrine of equivalents has an origin dating back to more than a century ago, while biotechnology patenting literally started with Chakrabarty in 1980. The judiciary may need more time to develop a line of case law in the area of biotechnology patent disputes.

Finally, this writer observes that the restraining effects of patent law, particularly the doctrine of equivalents, upon the improvement of a patented product and upon the advancement of biotechnologies, such as recombinant DNA technology, may be minimal. Although a third party may be deterred from doing research on a product, which may fall into the scope of equivalents of a patented product, a patent owner may still be interested in making any improvement on the patented product by using advanced technologies, such as recombinant DNA technology. The economic incentives of maximizing profits are high for the industry to improve existing products by using advanced technologies. New technologies bring high efficiencies and better quali-

224. Burk, supra note 5, at 82-85.
225. Id.
227. Id.
228. See supra note 4 and accompanying text.
ties to productions. Furthermore, an improved biological product can have more beneficial or better therapeutic effects which benefit the society in general.

VI. CONCLUSION

The dilemmas between the patent law and biotechnology have manifested in several federal district decisions, which would have restrained the advancement of biotechnology, as well as, the improvements of biological products. Nevertheless, the restraining effects are minimal.

In the meantime, the Federal Circuit Court of Appeals continues its endeavors of refining the methodology of analysis under the patent law, particularly the doctrine of equivalents, ever since the 1950 Graver Tank case. In 1987, an en banc decision in Pennwalt established an element-by-element equivalent analysis under the doctrine. In 1990, Wilson Sporting Goods suggested a “hypothetical claim” alternative for the equivalent analysis. Likewise, in a recent 1994 case, Federal Circuit ordered a rehearing en banc to decide a question of whether a finding of patent infringement under the doctrine of equivalents requires factors in addition to proof of the facts needed for the three-prong test.229

In Hormone Research, the trial court’s refusal to apply the doctrine of equivalents because of prosecution history estoppel would have relieved the recombinant HGH derivative from injunction and made it available to the public. A finding of infringement under the doctrine of equivalents will certainly prohibit the use of the recombinant Protropin by anyone else, a result which would be to the public’s detriment.

In Scripps, the appellate court correctly instructed that defendant Genentech could use the defense of reverse doctrine of equivalents, if the recombinant Factor VIII:C had better potency and purity than the patented Factor VIII:C in the product claim.230 Such instruction will be likely to relieve the recombinant Factor VIII:C from injunction and be made available to the public as well.

With respect to the holding on the issue of product-by-process claims in Scripps, the ruling would have unduly restricted the use of recombinant DNA technology to manufacture a product patented by a product-by-process claim having a different process. Fortunately, a

230. Supra note 194 and accompanying text.
Circuit judge panel in *Atlantic Thermoplastic* correctly rejected the *Scripps* holding on such issue and effectively narrowed the scope of a product-by-process claim, to the benefit of the biotechnology industry.

Likewise, Federal Circuit responded to the conceivable concerns from the biotechnology industry quite favorably in the recent *Wellcome* case. The trial court's broad interpretations under the doctrine of equivalents would have led to an injunction against FE1X, which has better therapeutic effects and less risk than the patented human t-PA to heart-attack patients. The appellate court in *Wellcome* wisely narrowed the three-prong test analysis under the doctrine of equivalents and made FE1X available to the public.

Thus, recent case law history has manifested a trend in that the Federal Circuit Court of Appeals has been endeavoring to resolve the dilemmas between the patent law and biotechnology. The *Wellcome* decision exemplifies such trend. It is wise to allow time for the judiciary to develop a line of cases in the area of biotechnology patenting.