# COMMENT

## PATENT PROTECTION FOR THE PROTEIN PRODUCTS OF RECOMBINANT DNA

BY SEAN JOHNSTON †

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† J.D. 1989, Stanford University; Ph.D. Molecular Biology 1985, University of California, Los Angeles; presently a law clerk for Judge Wm. Matthew Byrne, Jr., U.S. District Court, Los Angeles, California.

One of the most significant legal questions now confronting the biotechnology industry is the scope of protection that patents on so-called "first-generation" recombinant proteins will confer vis-a-vis "second-generation" analogs. These second-generation proteins may differ from the first-generation protein by as little as a single amino acid. Case law relating to traditional chemical inventions may give some insight into the approach that the Patent Office and courts will likely take in evaluating the issues of patentability and scope of patent protection for these recombinant protein products.

To the extent that inventors of first-generation recombinant proteins disclose the complete nucleotide sequence of the gene encoding the protein, strong arguments may be made that the invention is a pioneering one, entitled to broad patent protection. At the same time, if the patent system is to continue to serve the goal of promoting the invention of new and useful products, the opportunity to obtain patents on second-generation recombinant proteins must not be foreclosed. The pressing issue is where to draw the boundaries between the respective patent grants to ensure fair protection for everyone.

## I. INTRODUCTION

Biotechnology patent law has come a long way from the time when the patentability of recombinant microorganisms was at issue and the Supreme Court's landmark decision in *Diamond v. Chakrabarty*[1] was the focus of attention. Having overcome the initial difficulties in obtaining patent protection for the microorganisms used to produce recombinant proteins, the most significant legal questions now confronting the biotechnology industry concern the patenting of the recombinant protein products themselves. Of particular concern is the patentability of so-called "second-generation" recombinant proteins — analogs that may differ from the first-generation protein by as little a single amino acid — and the scope of protection that the patent on a first-generation recombinant protein will confer vis-a-vis the second-generation analogs.

These issues are of enormous practical importance to the biotechnology industry because of its reliance on patents to secure the economic returns on research and development investments.[2] The inventor of a second-generation recombinant protein seeks patent protection for his invention in order to obtain exclusive rights in the product and the monopoly rents that flow from it. At the same time, the inventor of the corresponding first-generation protein is intent on protecting the rights

1. 447 U.S. 303 (1980).

2. For a general discussion of the economic theory of property rights, see R. POSNER, ECONOMIC ANALYSIS OF THE LAW 28-75 (3d ed. 1986).

and rewards conferred by his patent grant from appropriation by competitive late-comers. The ultimate resolution of the issues concerning patent rights in first- and second-generation recombinant proteins may largely shape the course of future research and development efforts in biotechnology.[3]

## A. The Fundamentals of Molecular Biology

In the same way that the advent of semiconductor technology heralded a revolution in electronics, biotechnology has heralded a revolution in the pharmaceutical industry, the results of which are now only beginning to be realized.[4] A recent analyst's report even suggested that existing pharmaceutical firms will evolve into biopharmaceutical firms in the 1990s, thus resulting in the technological, if not financial, acquisition of the pharmaceutical industry by the biotechnology industry.[5]

The business of biotechnology is founded on the science of molecular biology — the study of the genetics of living organisms at the molecular level — and in particular, those methods that characterize recombinant DNA technology.[6] Recombinant DNA techniques make it possible for researchers to move genetic material in a functional form from one organism to another, creating genetic constructs that have never before existed in nature. For instance, the gene that produces a protein such as insulin can be isolated from human cells and inserted into another host cell, such as a bacterium. The bacterium can then be

3. "[T]he basic policy underlying the patent system is to encourage the disclosure of inventions through issuance of patents. Another policy of the system is to stimulate the investment of risk capital in the commercialization of useful patentable inventions so that the public gets some benefit from them, which may not occur in the absence of some patent protection." Rohm and Haas Co. v. Crystal Chemical Co., 722 F.2d 1556, 1571 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). *See also, e.g.*, Kitch, *The Nature and Function of the Patent System*, 20 J. LAW & ECON. 265 (1977); Plant, *The Economic Theory Concerning Patents for Inventions*, 1 ECONOMICA 30 (1934).

4. The first pharmaceutical produced through recombinant DNA technology to be approved by the U.S. Food and Drug Administration (FDA) and to be marketed was human insulin. FDA approval came in October 1982 and commercial sales began shortly thereafter. *As Lilly's Synthetic Insulin Gets FDA OK, Novo, Biogen Join to Clone Their Own*, McGraw Hill's Biotechnology Newswatch, Nov. 15, 1982, at 2; Johnson, *Human Insulin from Recombinant DNA Technology*, 219 SCIENCE 632 (1983). As of 1989, a total of nine biotechnology-based pharmaceuticals have been approved for commercial use by the FDA. Gupta, *Watching and Waiting: Biotechnology Holds Great Promise, but Investors are Still Waiting for the Payoff*, Wall St. J., Nov. 13, 1989, at 32, col. 1.

5. ARTHUR YOUNG HIGH TECHNOLOGY GROUP, *Introduction* to BIOTECH 88: INTO THE MARKETPLACE at 2 (1987).

6. For general references, see K. DRLICA, UNDERSTANDING DNA AND GENE CLONING (1984); J. WATSON, J. TOOZE & D. KURTZ, RECOMBINANT DNA, A SHORT COURSE (1983) [hereinafter J. WATSON]; Gilbert and Villa-Komaroff, *Useful Proteins from Recombinant Bacteria*, SCI. AM., Apr. 1980, at 74.

reproduced or cloned, creating many identical copies of the gene. If the gene can then be coaxed to manufacture the same protein in bacteria that it does in a human cell, large quantities of the protein can be produced for pharmaceutical applications.[7]

The gene that is expressed in the host cell consists of a defined segment of deoxyribonucleic acid (DNA). DNA is the basic hereditary component of all living matter and contains all the information needed to make the organism and carry on its functions, including complete instructions on what proteins to produce.

DNA is itself a duplex molecule—a so-called "double helix"—formed by the annealing of two nucleic acid polymers. Each nucleic acid polymer, or "strand," of the DNA molecule is assembled from chemical building blocks called nucleotides. Each nucleotide contains a phosphate group linked to a sugar molecule which, in turn, is joined to one of the following four chemicals: adenine (A), thymine (T), guanine (G), or cytosine (C). These four chemicals are called "nucleotide bases." The formation of the double-stranded DNA molecule results from the inherent property of nucleic acid polymers to combine with one another through "complementary base pairing," by which an A on one strand becomes "base-paired" with a T on the other strand, and a G with a C.

The specific sequence of the nucleotide bases along a strand of DNA encodes the information necessary to produce a protein.[8] A cell's protein synthesis machinery "reads" the sequence of nucleotide bases in groups of three, called "codons." Each of the 64 possible codons (which constitute all of the possible combinations of triplet base sequences) corresponds to a particular amino acid or acts as a signal to start or stop protein synthesis. Amino acids are the building blocks of proteins. Just as the sequence of codons within a gene specifies the sequence of amino acids in a protein, the sequence of amino acids within the protein

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7. *See, e.g.*, Goeddel, Kleid, Bolivar, Heyneker, Yansura, Crea, Hirose, Kraszewski, Itakura & Riggs, *Expression in Escherichia coli of Chemically Synthesized Genes for Human Insulin*, 76 PROC. NAT'L ACAD. SCI. USA 106 (1979); Johnson, *supra* note 4.

Proteins are the basic components of biological structures and processes. Familiar structural proteins include collagen, which forms connective tissues such as cartilage and bone, and keratin, which forms skin and hair. Examples of proteins that carry out biological processes are insulin, which regulates sugar metabolism; Factor VIII, which is needed for blood clotting; and antibodies, which help protect against infection by foreign substances. Given the range of apparent medical uses of proteins, their production in pure quantities has been and continues to be one of the principal objectives of biotechnology.

8. For general references, see 1 J. WATSON, N. HOPKINS, J. ROBERTS, J. STEITZ & A. WEINER, MOLECULAR BIOLOGY OF THE GENE 81-87 (4th ed. 1987); B. LEWIN, GENES 37 (3d ed. 1987).

specifies the physical structure of the protein and its characteristic functional properties.

The production of a desired protein in a foreign host cell requires two basic steps: 1) identifying and isolating the gene encoding the desired protein; and 2) transferring the gene into the host cell. In general, the first step is by far the most difficult.[9] Identifying the gene for a specific protein typically requires that at least a part of the nucleotide sequence of the gene be known. In most cases, this will involve inferring the nucleic acid sequence from the amino acid sequence of the protein. Although the techniques for amino acid sequencing are well known, obtaining a sample of the protein in sufficient quantity and purity for analysis can be quite difficult. Indeed, the decision to produce a protein by the methods of recombinant DNA technology is often motivated by the fact that such limited quantities of the protein are available from natural sources.[10]

Once a portion of the sequence of the gene is determined, a short single-stranded nucleic acid "oligonucleotide" may be synthesized having a nucleotide sequence complementary to the derived genetic sequence. Then that oligonucleotide may be used as a "probe" for isolating the gene from a natural source.[11] Conceptually, the process of using an oligonucleotide probe to isolate a desired gene is analogous to searching for a needle in a haystack. Because of the quantity and complexity of DNA in the cells of living organisms, isolating a single gene entails picking out a specific sequence of hundreds or thousands of nucleotides from amongst a total of perhaps several billion nucleotides.[12] As Philip Leder of Harvard Medical School has described it, "[i]f we took the DNA . . . from a single human cell and laid it out, it would be about one meter in length. If we could stretch that meter into one kilometer, a single gene would be represented in a millimeter's worth of DNA."[13] The individual intent on being the first to express a specific human protein

9. The relative difficulty of identifying and isolating the gene for a desired protein is a consequence of the complexity of the natural environment in which the gene and protein are found. For example, the DNA in each human cell consists of a total of about 3 billion nucleotide base pairs, organized into 100,000 or more individual genes. *See generally*, J. WATSON *supra* note 6.

10. *See* OFF. OF TECH. ASSESSMENT, COMMERCIAL BIOTECHNOLOGY: AN INTERNATIONAL ANALYSIS, U.S. Cong., Pub. No. OTA-BA-218 at 119-136 (1984).

11. *See, e.g.*, Wood, Capon, Simonsen, Eaton, Gitschier, Keyt, Seeburg, Smith, Hollingshead, Wion, Delwart, Tuddenham, Vehar & Lawn, *Expression of Active Human Factor VIII from Recombinant DNA Clones*, 312 NATURE 330, 331-32, 334 (1984) (describing the use of synthetic oligonucleotides to isolate the gene for human Factor VIII).

12. *See supra* note 8.

13. S. OLSON, BIOTECHNOLOGY - AN INDUSTRY COMES OF AGE 16 (1986).

by recombinant DNA technology must locate the correct millimeter along the kilometer course.

## B. The Fundamentals of Patent Law

Because of the tremendous investments of labor and capital required to produce "first-generation" recombinant proteins[14] — those resulting from the identification, isolation, and expression of a native cellular gene — it is not surprising that the biotechnology industry has aggressively sought patent protection for its efforts.[15]

To be patented, a product must satisfy the three statutory requirements of utility, novelty, and non-obviousness, found in Title 35 of the United States Code.[16] The utility requirement ensures that the invention is useful for some purpose.[17] To be novel, the invention must be new, so that a patent is not granted for something that already belongs to the public.[18] The non-obviousness requirement extends the novelty requirement and ensures that a person skilled in the relevant art cannot take something in the public domain, make a trivial change in it, and receive a patent for the result.[19]

In the case of a first-generation recombinant protein, utility is a foregone conclusion since the recombinant protein will at least serve the same useful purpose as its naturally occurring counterpart. Furthermore, a first-generation recombinant protein may be considered novel and hence patentable despite the existence of the naturally occurring protein, so long as the recombinant protein exhibits some property lacking in the naturally occurring protein, such as purity or potency.[20] The non-obviousness of a first-generation recombinant protein may be established, for example, by showing the unpredictable nature of the methods used to produce it, or by showing that the protein was not pre-

14. For example, securities analysts estimate that Genentech, Inc. expended over $200 million to bring a recombinant tissue plasminogen activator to market. Bylinsky, *Genentech Has a Golden Goose*, FORTUNE, May 9, 1988, at 52, 62.

15. One measure of importance of patents to the biotechnology industry is the number of biotechnology-related patent applications that are filed. As of September 1988, some 15,000 to 16,000 biotechnology-related patent applications were pending in the U.S. Patent and Trademark Office (PTO), "with more coming in all the time." *New Legal Species Born of Biotech*, Insight, Sept. 19, 1988, at 54-55. Another measure is the frequency of biotechnology-related patent litigation, see Appendix A.

16. 35 U.S.C. §§ 101-103 (1982).

17. 35 U.S.C. § 101 (1982).

18. 35 U.S.C. § 102 (1982).

19. 35 U.S.C. § 103 (1982).

20. *See, e.g., In re* Bergstrom, 427 F.2d 1394, 1401 (C.C.P.A. 1970) (where compound does not exist in nature in pure form, pure compound is patentable).

viously known to exist in nature.[21] Pursuant to this statutory scheme, United States patents have already been granted for a number of first-generation recombinant proteins.[22]

In addition to the statutory requirements of novelty, utility, and non-obviousness, 35 U.S.C. § 112, first paragraph, requires that a patent: (i) provide a written description of the invention; (ii) disclose how to make and use the invention; and (iii) disclose the best mode for carrying out the invention.[23] As a means of complying with the enablement and best mode requirements, the patent on a first-generation recombinant protein will typically disclose the complete nucleotide sequence of the gene used to produce the protein.[24]

For the patentee, obtaining the nucleotide sequence of the isolated gene is straightforward and involves routine methodologies. However, in the hands of a competitor, such information is of incalculable value. Not only does the sequence information teach one how to make and use the underlying invention — the first-generation recombinant protein — it also enables one to produce a whole host of second-generation proteins.

Starting with the sequence of the gene for the first-generation protein, a competitor can isolate that gene and then, using the disclosed nucleotide sequence as a guide, selectively make changes in the isolated gene.[25] Changes in the nucleotide sequence produce changes in the amino acid sequence of the protein. As a practical matter, therefore, the disclosure of the nucleotide sequence for the first-generation recombinant protein places anyone of ordinary skill in the art of molecular biology in the business of producing second-generation analogs of the first-generation protein.

A recent European patent application relating to "Novel Human TNF Polypeptide Mutants and DNAs Encoding Said Mutants"[26]

21. *In re* O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988); *Ex parte* Old, 229 U.S.P.Q. 196 (Bd. Pat. App. & Int. 1985).

22. *See, e.g.*, U.S. Patent No. 4,879,226, issued Nov. 7, 1989 (human tumor necrosis factor); U.S. Patent No. 4,659,805, issued Apr. 21, 1987 (human alveolar surfactant protein); U.S. Patent No. 4,658,021, issued Apr. 14, 1987 (human growth hormone); U.S. Patent No. 4,632,981, issued Dec. 30, 1986 (human antithrombin III).

23. The first paragraph of section 112 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112 (1982).

24. *See supra* note 22.

25. One method for making nucleotide changes in an isolated gene is referred to as site-directed mutagenesis. This method is used to introduce pre-determined nucleotide changes at specific sites within the isolated gene. *See generally* J. WATSON *supra* note 6.

26. European Patent Application No. 0251037, filed June 16, 1987.

provides a dramatic example of the potential that exists for developing analogs of first-generation proteins. Starting with the previously disclosed sequence of the gene for human tumor necrosis factor (TNF), a protein that may be useful in treating cancer, the inventors systematically altered the gene to produce hundreds of different analogs of TNF, each differing from native TNF by a single amino acid substitution. The first two claims of the patent application are shown in Appendix B. The pressing issue for the Patent Office is how to evaluate the patentability of such recombinant protein analogs in light of the sequence disclosures of the first-generation proteins.

## II. PATENTING SECOND-GENERATION RECOMBINANT PROTEINS IN THE UNITED STATES

To be patentable in the United States, a second-generation recombinant protein analog must satisfy the same statutory requirements of utility, novelty, and non-obviousness as does the first-generation protein.[27] The utility requirement may be satisfied simply by showing that the second-generation protein retains or improves upon some functional property of the first-generation protein. The analysis of the novelty and non-obviousness of the analog will differ, however, from that carried out for the first-generation protein because the patent on the first-generation protein will be available as a "prior art" reference.[28]

### A. Novelty

In order for a prior art reference to "anticipate" and therefore negate the novelty of a later claimed invention, the reference must identically describe or disclose the invention in such a manner as to place it in

27. *See* 35 U.S.C. §§ 101-103 (1982). For purposes of the present discussion, the analogs of interest are those that emulate or improve upon the first-generation protein, and will therefore be assumed to satisfy the utility requirement of 35 U.S.C. § 101. *See supra* note 20 and accompanying text.

28. The term "prior art" refers to at least the statutory prior art material named in 35 U.S.C. § 102. *In re* Yale, 347 F.2d 995, 1000 (C.C.P.A. 1965). Section 102 states in pertinent part:

> A person shall be entitled to a patent unless —
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
>
> . . .
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent. . . .

Thus, the patent on the first-generation protein may be considered prior art under 35 U.S.C. § 102(a) (patent reference is prior art as of its date of issue), or § 102(e) (United States patent reference is prior art as of the date of filing).

the public domain.[29] Determining whether a patent on a first-generation recombinant protein anticipates a particular analog thus requires a consideration of whether the analog is "described" in the patent within the meaning of 35 U.S.C § 102.[30]

Given the breadth of the disclosures that may be found in a patent on a first-generation recombinant protein,[31] the question of whether a particular analog has been described for purposes of section 102 can easily deteriorate into one of semantics. For example, if the mere contemplation of making "minor modifications of [the] primary amino acid sequence"[32] of the first-generation protein were considered to be an adequate description, then the typical patent on a first-generation protein would render countless analogs unpatentable.

Although there have been no decisions to date on whether a broad generic disclosure of analogs of a first-generation recombinant protein will anticipate later claims to specific analogs encompassed by the generic disclosure, the Patent Office and courts have previously struggled with the same sort of issue in cases involving traditional chemical compounds. Those cases have held that the patenting of a broad chemical genus, embodying hundreds or thousands of possible chemical compounds, will not prevent others from obtaining patents on the individual compounds.[33]

In *In re Arkley*[34] for example, the court reversed the Patent Office's decision that the appellants' claim to a specific antibiotic compound was anticipated by virtue of having been one of the over 230,000 compounds embraced within the generic claim of an existing patent. As far as the court was concerned, such a broad disclosure, "pointing to no particular

29. *In re* Arkley, 455 F.2d 586, 587 (C.C.P.A. 1972); *In re* Brown, 329 F.2d 1006, 1011, (C.C.P.A. 1964); *In re* LeGrice, 301 F.2d 929, 930, (C.C.P.A. 1962).

30. In the following discussion, it will be assumed that the only prior art in existence at the time of the invention of the second-generation protein is the patent on the first-generation protein. *See supra* note 28.

31. *See, e.g.*, U.S. Patent No. 4,659,805, issued Apr. 21, 1987:

> [M]inor modifications of [the] primary amino acid sequence [of alveolar surfactant protein (ASP)] may result in proteins which have substantially equivalent or enhanced activit[ies.] . . . These modifications may be deliberate, as through site-directed mutagenesis, or may be accidental, such as through mutation of hosts which are ASP producing organisms. All of these modifications are included [within the scope of the invention] as long as the ASP activity is retained.

32. *Id.*

33. *See, e.g., In re* Ruschig, 343 F.2d 965, (C.C.P.A. 1965) (prior art references that claimed a group of 259 compounds did not anticipate claims to four specific compounds of that group where the prior art did not specifically describe the later compounds).

34. 455 F.2d 586 (C.C.P.A. 1972).

one of the myriads of compounds, actual and potential,"[35] was not the sort of description required by section 102:

> [F]or the instant rejection under 35 U.S.C. § 102(e) to have been proper . . . [the patent] reference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference.[36]

Also instructive are those cases involving a prior art patent reference with claims directed to a general chemical formula and a vast number of possible substituents, which also discloses a more limited class of "preferred" compounds. Where a third-party has later sought to patent one of the preferred compounds and has been able to establish that the compound has some unexpected property not attributed to it by the prior art patent, the courts have refused to treat the earlier patent disclosure as an anticipation.[37]

These decisions reflect a trend by the courts to narrowly interpret section 102, so as to preclude a finding of anticipation in most instances except where the compound for which a patent is sought is individually disclosed in the prior art, or is disclosed as a member of "a small recognizable class [of compounds] with common properties."[38]

The unwillingness of the courts to apply section 102 any more expansively seems to be motivated by two related policy concerns. First, because claims to a broad genus or class of compounds can be more a product of wishful thinking and creative writing than actual invention, the patentee may be unjustly rewarded by the grant of exclusive rights to every compound encompassed by such claims. Second, denying patentability to a specific compound, solely on the grounds that it was disclosed as one of a large group of compounds, may quash the incentive of others to identify and develop those individual compounds which may possess unexpected beneficial properties. As the court stated in *In re Wiggins*:

> The mere naming of a compound in a reference, without more, cannot constitute a description of the compound. . . . If we were to hold otherwise, lists of thousands of theoretically possible compounds could be generated and published which, assuming it would be within the level of skill in the art to make them, would bar a patent to the actual discoverer of a named compound no matter how beneficial to mankind it might be. In view of the fact that the

35. *Id.* at 588.

36. *Id.* at 587 (emphasis in the original).

37. *In re* Kalm, 378 F.2d 959, 963 (C.C.P.A. 1967); *In re* Ruschig, 343 F.2d 965 (C.C.P.A. 1965).

38. *Ruschig*, 343 F.2d at 974.

> purpose sought to be effectuated by the patent law is the encouragement of innovation, such a result would be repugnant to the statute.[39]

Those same concerns apply to the products of recombinant DNA technology and provide strong support for the argument that the Patent Office and courts should strictly interpret what is "described" in a patent on a first-generation recombinant protein for purposes of 35 U.S.C. § 102. Otherwise, to allow the sweeping language of the patent on a first-generation protein to dictate the patentability of its analogs would inevitably reduce the incentive of others to invest in the research and development of second-generation proteins. This, in turn, might deprive the public of some of the most beneficial products of biotechnology. While there can be no doubt that the patentee of a first-generation protein is entitled to ample reward for his invention, it certainly should not come at such tremendous public cost.

## B. Non-Obviousness

### 1. *The Traditional Analysis*

Assuming that a useful recombinant protein analog is not anticipated by the patent on the corresponding first-generation protein (or other prior art) and therefore satisfies the novelty requirement of 35 U.S.C. § 102, the final test of its patentability is the non-obviousness requirement of 35 U.S.C. § 103. Section 103 states:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Congress adopted section 103 as part of the 1952 Patent Act to formalize the concept of non-obviousness and to introduce some consistency into what had become a highly variable standard of patentability.[40] However, by failing to specify exactly how obviousness was to be determined, Congress left the Patent Office and courts to fend for themselves once again. As might be expected, the results were somewhat haphazard.

In its first interpretation of the 1952 Patent Act, the Supreme Court tried to clarify the law by setting forth the general approach to be

39. *In re* Wiggins, 488 F.2d 538, 543 (C.C.P.A. 1973).
40. Graham v. John Deere Co., 383 U.S. 1, 12-17 (1966).

taken by the Patent Office and the courts in applying section 103.[41] While stating that the ultimate question of patentability is one of law, the Court said that the question of non-obviousness was necessarily informed by a three-step process of factual inquiry:

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.[42]

As to the apportionment of responsibility between the Patent Office and the courts in interpreting section 103, the Court stated that the Patent Office should strictly adhere to the analysis indicated by the Court, and should assume "primary responsibility for sifting out unpatentable material."[43] The proper role of the courts was to interpret and elaborate the standards of non-obviousness on a case-by-case basis — a responsibility that the Court then recognized would pose practical difficulties.[44]

However well this approach has worked with mechanical inventions, the assessment of non-obviousness of chemical compounds has proven to be a never-ending source of controversy,[45] and there is every reason to expect that the same will be true with recombinant proteins. The advent of biotechnology is not likely to provide the impetus for a complete rewriting or reinterpretation of section 103. Thus, the challenge for the Patent Office and the courts is to adapt and expand the well-established legal doctrine involving traditional chemical compounds to apply to the protein products of recombinant DNA technology.[46]

As with any traditional chemical compound, it is possible to assess the non-obviousness of a recombinant protein analog on the basis of either its physical structure or its functional properties. If the non-

41. *Id.* at 17-19.
42. *Id.* at 17.
43. *Id.* at 18.
44. *Id.*
45. *See, generally,* 2 CHISUM, PATENTS § 5.04[6] (1989).
46. The non-obviousness determination under 35 U.S.C. § 103 is similar to the question of what analogs are described in the patent on a first-generation protein for novelty purposes under 35 U.S.C. § 102. That is, what analogs are taught or suggested to one of ordinary skill in the art by the disclosures of the patent on a first-generation protein? In evaluating the non-obviousness of a protein analog based on its functional properties, the relevant prior art would not necessarily be limited to the patent on the first-generation protein. To the extent that other materials and knowledge in the public domain taught or suggested the functional properties of the protein analog, those would also be considered under the analysis set forth in *Graham v. John Deere.* In the following discussion, however, it will be assumed that the only prior art in existence at the time of the invention of the second-generation protein is the patent on the first-generation protein.

obviousness of a protein analog were determined solely on the basis of its structure, the test under section 103 would presumably be reduced to a rather mechanistic overlaying of amino acid sequences. According to such a test, virtually any analog of a first-generation recombinant protein might be considered obvious, and hence unpatentable.[47] The argument would be that since any molecular biologist could make changes in the gene sequence of the first-generation protein to produce any conceivable protein structure, the resulting protein analogs must be obvious. Perhaps the only debate would be at what point the alterations made to the protein structure become so extensive that the analog begins to look less like an analog of the first-generation protein and more like some other protein.

On the other hand, if the non-obviousness of an analog were assessed on the basis of its functional properties, a much more sophisticated inquiry would be required. The issue would be not whether a molecular biologist could conceive of making a particular analog given the disclosures of the patent on the first-generation protein, but whether someone of ordinary skill in the art could predict with a reasonable degree of certainty what properties the analog would possess. According to this test, a protein analog would be non-obvious, notwithstanding its structural similarity to the first-generation protein, if the analog could be shown to possess some unexpected, non-obvious property.

The Patent Office and the courts have taken the latter of these approaches in evaluating the non-obviousness of traditional chemical compounds. The leading case of *In re Papesch*[48] held that more than just the chemical structure of a compound must be considered in evaluating non-obviousness.

The *Papesch* patent application claimed certain compounds possessing potent anti-inflammatory properties. The Patent Office rejected the claimed compounds as obvious in view of their close structural similarity to several prior art compounds, despite evidence that the structurally similar prior art compounds had no anti-inflammatory activity. The court reversed the decision of the Patent Office, holding that a fundamental error of law had been committed in failing to consider the unexpected biological or pharmaceutical property of a "structurally obvious" chemical compound as evidence of its non-obviousness:

47. Thus, a test of obviousness based solely on a comparison of amino acid sequences would have the same practical effect as finding the analog to be "described" for purposes of section 102 by a broad generic claim in the patent on the first-generation protein.

48. 315 F.2d 381 (C.C.P.A 1963).

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. . . . [W]hile [a structural formula] may serve in a claim to identify what is being patented, as the metes and bounds of a deed *identify* a plot of land, the *thing* that is patented is not the formula but the compound identified by it.[49]

Under the *Papesch* doctrine, the non-obviousness of a chemical compound is to be determined by a consideration of all aspects of the claimed compound—its structure as well as its properties. Where the Patent Office makes out a *prima facie* case of obviousness on the basis of the close structural similarity of the claimed compound to a prior art compound, the *prima facie* case may be rebutted by evidence that the claimed compound has unexpected beneficial properties.[50] In general, such rebuttal evidence has been of two types: evidence of a property in the claimed compound not present in the prior art compound,[51] and evidence that the claimed compound is unexpectedly superior in a property it shares with a prior art compound.[52]

Applying these same principles to the case of a recombinant protein, the non-obviousness of an analog of a first-generation protein could be established in a number of ways. For example, evidence that the analog is more potent than the first-generation protein, that the analog produces fewer deleterious side effects than the first generation protein, or that the analog possesses some utility altogether lacking in the first-generation protein, could establish the non-obviousness of the analog. In each instance, the Patent Office, and perhaps ultimately a court, must determine whether an actual difference in properties between the analog and the first-generation protein exists, and if so, whether the difference would have been unexpected or non-obvious to one possessing ordinary skill in the art.

One issue not addressed in *Papesch*, however, which may prove to be especially troublesome in the case of recombinant proteins, is how to judge the difference in properties between a claimed analog and a structurally similar prior art compound when the two share significant properties in common. Individual proteins may possess multiple functional properties due to the presence of separate "functional domains" within the structure of the protein molecule.[53] An antibody molecule, for example, possesses at least three functional domains, one responsible for the binding of an antigen, and two which coordinate the interaction of

49. *Id.* at 391 (emphasis in the original).

50. *Id.* at 386-37.

51. *In re* Kalm, 378 F.2d 959 (C.C.P.A. 1967).

52. *In re* Chupp, 816 F.2d 643 (Fed. Cir. 1987); *In re* Ackermann, 444 F.2d 1172 (C.C.P.A. 1971); *In re* Lunsford, 357 F.2d 380 (C.C.P.A. 1966).

53. For general references, see *supra* note 8.

the antibody with other components of the immune response.[54] Another example is tissue plasminogen activator (tPA), an enzyme known for its activity in dissolving blood clots, which has separate functional domains for binding the protein to a blood clot and for triggering clot lysis.[55]

If a novel recombinant protein analog differs unexpectedly from the first-generation protein in one aspect, but otherwise retains all of the functional properties of the first-generation protein, should the analog be considered non-obvious? The answer to this question should be an unequivocal "yes." However, in several cases decided after *Papesch,* courts have held that the existence of significant common properties may preclude a patent on a structurally obvious chemical compound.[56] Later decisions indicated that the unexpectedly different properties of the claimed compound should be "balanced" against the common properties in order to make the ultimate determination of non-obviousness.[57]

If this "balancing" analysis were followed in determining the patentability of recombinant protein analogs, several common properties shared between the prior art protein and the recombinant analog would likely outweigh a single unexpected property of the analog. It is conceivable that analogs of all but the simplest "single function" proteins would be considered obvious. This result would have serious adverse consequences for the biotechnology industry without an apparent countervailing public policy justification. What possible purpose can be served by denying a patent on a protein analog that possesses a concededly unexpected beneficial property simply because other properties of the analog are indistinguishable from the first-generation protein?

The Patent Office has expressed concern on a number of occasions that allowing a patent on a structurally obvious chemical compound,

54. *See generally,* B. LEWIN, *supra* note 8.

55. Holvoet, Lijnen, & Collen, *Characterization of Functional Domains in Human Tissue-Type Plasminogen Activator with the Use of Monoclonal Antibodies,* 158 EUR. J. BIOCHEM. 173 (1986).

56. *In re* De Montmollin, 344 F.2d 976, 978 (C.C.P.A. 1965). *See also* Carter-Wallace, Inc. v. Davis-Edwards Pharmaceutical Corp., 341 F. Supp 1303, 1339 (E.D.N.Y. 1972), *aff'd,* 474 F.2d 529, 546 (2d Cir. 1972), *cert. denied,* 412 U.S. 929 (1973) ; *In re* Mod, 408 F.2d 1055, 1057 (C.C.P.A. 1969) (an unexpected activity in an analog was not sufficient to overcome an obviousness rejection where the compound was structurally similar to prior art compounds, because the prior art compounds also possessed the activity, but this fact had not been previously known).

57. *In re* May, 574 F.2d 1082, 1093 (C.C.P.A. 1978); *see also* Warner-Jenkinson Co. v. Allied Chem. Corp., 477 F. Supp 371, 388 (S.D.N.Y. 1979), *aff'd,* 633 F.2d 208 (2d Cir. 1980) ("courts have been moving to a test of 'essential predictability,' balancing the significance of unexpected properties resulting from minor chemical manipulations of existing compounds against the desirable properties that would be expected from such alterations").

based on evidence of a single unexpected property, would improperly allow the patentee to "dominate" any other activity which the claimed compound shared with the structurally similar prior art compound—"activity wholly unrelated to the property argued. . . ."[58] Such concern, however, is misguided. A patent on an analog that possesses some unexpected beneficial property would not take from the public that which is already theirs, or impose on them a monopoly that should not exist.[59] Even if such an analog shares significant properties in common with a prior art compound, the patent on the analog will not dominate those shared properties for the simple reason that the public's access to the first-generation protein remains unaffected.

Assuming that the analog and the first-generation protein possess different functional properties, the Patent Office must finally determine whether the difference is one that would have been obvious to someone of ordinary skill in the art.[60] In other words, for the difference in properties to make the analog patentable, the difference must be something that could not have reasonably been expected from a knowledge of the prior art at the time the analog was made.

Although much is known in the subjects of molecular biology and protein biochemistry, there is certainly much more that remains unknown. One particular area where knowledge is lacking is in predicting the functional properties of a protein from its structure.[61] It is well known that even minor changes in amino acid sequence can dramatically alter a protein's function. For example, sickle-cell anemia, an inherited blood disorder, results from a single amino acid substitution in a hemoglobin protein.[62] Also, some scientists now suspect that single amino acid changes may endow otherwise normal human proteins with cancer-producing properties.[63]

58. *In re* Ruschig, 343 F.2d 965, 978 (C.C.P.A. 1965). As suggested by the quote from *Ruschig*, under the patent laws of the United States, a patent on a compound confers rights to every use of which the compound is susceptible. *In re* Thuau, 135 F.2d 344, 347 (C.C.P.A. 1943). Thus, the granting of a patent for an analog of a multifunctional protein would secure to the patentee rights in all the properties of the analog, including those identically shared with the first-generation protein.

59. The only injustice that might result would be if the patent on the analog were held not to infringe an existing patent on the prior art compound. Under such circumstances, the patentee of the analog could freely make, sell, and use the analog for any purpose, including any utility shared with the first-generation protein, in direct competition with the prior art compound. As discussed *infra*, section III, the injustice of such a result lies not in the granting of the patent on the analog, but rather in the failure to provide an adequate scope of patent protection on the prior art compound.

60. 35 U.S.C. § 103 (1982); Graham v. John Deere Co., 383 U.S. 1, 17 (1966).

61. Van Brunt, *Beta Barrels, Helix Bundles, Hairpin Turns, and Pleated Sheets*, 6 BIO/TECHNOLOGY 655 (1988).

62. *See* J. WATSON, *supra* note 8, at 78-79.

63. *See* Bishop, *The Molecular Genetics of Cancer*, 235 SCIENCE 305 (1987).

While substantial progress is being made in developing computer models of how specific amino acid changes affect the structure of a protein, scientists are still a long way from predicting how a change in the structure of a protein will affect its function. Even where the three-dimensional structure of a protein is known from x-ray crystallography, the choice of where to make changes in the structure to achieve desired effects is still a matter of trial and error.[64]

Thus, it certainly cannot be said at this point that the disclosure of the nucleic acid sequence of the gene encoding the first-generation protein inherently reveals the properties of any specific analog, nor can knowledge of the first-generation protein's properties offer any more than a suggestion of what to expect in the analog. As the court stated in *Eli Lilly and Co. v. Generix Drug Sales, Inc.*:

> Except where the state of the medical art and the state of the chemical art have been advanced and coordinated to the point that it is possible for the mind to conceive or predict with some minimal reliability a correlation between chemical analogues, homologues or isomers and their therapeutic value, reason compels us to agree that novelty, usefulness, and non-obviousness inhere in the true discovery that a chemical compound exhibits a new needed medicinal capability, even though it be closely related in structure to a known or patented drug.[65]

Until scientific understanding of protein structure-to-function relationships improves, so that one can predict the functional effects of changes in a protein's amino acid sequence, the discovery of improved properties in an analog as compared to the first-generation protein should render the second-generation analog non-obvious.

### 2. *Proposal for a Formal Rule of Per Se Non-Obviousness*

In *Papesch*, the court discussed the problem of determining obviousness:

> [t]he problem of "obviousness" under section 103 in determining the patentability of new and useful chemical compounds . . . is not really a problem in chemistry or pharmacology or in any other related field of science such as biology, biochemistry, pharmacodynamics, ecology, or others yet to be conceived. It is a problem of *patent law*.[66]

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64. *See, e.g.*, Van Brunt, *supra* note 61; *Crystallographers, Gene-Splicers Remodeling Subtilisin*, McGraw-Hill's Biotechnology Newswatch, Jan. 6, 1986, at 2; Blundell & Sternberg, *Computer-Aided Design in Protein Engineering*, 3 TRENDS IN BIOTECHNOLOGY 228 (1985); Winter & Fersht, *Engineering Enzymes*, 2 TRENDS IN BIOTECHNOLOGY 115 (1984); Wilson & Klausner, *Computers Reveal Proteins' Mysteries*, 2 BIO/TECHNOLOGY 511 (1984).

65. Eli Lilly & Co. v. Generix Drug Sales, Inc., 460 F.2d 1096, 1103 (5th Cir. 1972).

66. *In re* Papesch, 315 F.2d 381, 386 (C.C.P.A. 1963) (emphasis in original).

It is difficult to regard that statement today without a certain degree of skepticism, considering the technical complexity of the evidence on which the Patent Office must base its determination of obviousness. In the case of a recombinant protein analog, it may be necessary for a patent examiner to interpret comparative studies of an analog's properties and those of the first-generation protein. If differences exist, then she must review patent references and scientific literature in molecular biology, protein biochemistry, physiology, and pharmacology, to discern whether the prior art would lead one skilled in the art to predict the analog's properties.

While this approach is not conceptually different from that which the Patent Office undertakes in reviewing other patent applications, the practical difficulties of engaging in such detailed analysis for each of the multitude of recombinant protein analogs for which patent applications have been filed, are substantial.

The total backlog of pending biotechnology patent applications in the U.S. Patent Office as of May 1989 stood at 14,783.[67] Because of this backlog, applicants must now wait about thirteen months before an examiner even looks at an application, and another thirteen months before a final decision is issued.[68] This backlog is more than just a nuisance. According to a number of experts, the backlog in biotechnology-related patent applications is undermining the viability of the biotechnology industry.[69] If only to reduce the potential for an even more severe backlog in biotechnology patent applications, it is reasonable to consider whether there might be an alternative to the present approach for evaluating the patentability of recombinant protein analogs.

One possibility worthy of serious consideration is for the Patent Office to adopt a formal rule of *per se* non-obviousness for novel protein analogs. Such an approach may sound like a radical departure from the established criteria of patentability developed in *Papesch* and its progeny. However, there are good reasons to believe that a rule of *per se* non-obviousness would achieve similar results to those reached under the traditional analysis.

The concern evoked by a rule of *per se* non-obviousness is that patents will be sought and issued for analogs that would have otherwise

67. J. Kittle, Materials from the Board Meeting of the Biotechnology Institute, U.S. Patent and Trademark Office (July, 1989) (available at the *High Technology Law Journal* Office).

68. *Id. See also* Crawford, *Patent Claim Buildup Haunts Biotechnology*, 239 SCIENCE 723 (1988).

69. Yoo, *Biotech Patents Become Snarled in Bureaucracy*, Wall St. J., July 6, 1989, sec. 2 at 1, col. 6. *See also* Merges, *Congress Expresses Concern over Backlog of Biotech Patent Applications*, Genetic Engineering News, June 1988, at 3, col. 1.

been found obvious and unpatentable. Such analogs fall into two categories: analogs with properties indistinguishable from the first-generation protein, and analogs whose properties, though different from the first-generation protein, are made obvious by the prior art.

With respect to the first group of analogs, it is doubtful whether anyone would even go to the trouble of filing a patent application. Considerable expense would be incurred in drafting and prosecuting a patent application which, once issued as a patent, in all likelihood would subject the applicant or his assignee to an infringement action by the owner of the patent on the corresponding first-generation protein.[70]

With respect to the second group of analogs, perhaps the complete answer to the concern over such proteins being *per se* non-obvious is to point out that such obvious analogs simply do not exist, and will not exist until the predictability of protein structure-to-function relationships is substantially more advanced. Accordingly, the Patent Office's demanding, case-by-case examination of applications for patents on recombinant protein analogs for compliance with section 103 seems entirely out of step with the realities that affect the decision to file for a patent and the practical limitations of the relevant technology.

Moreover, a strong argument may be made that a rule of *per se* non-obviousness is in fact compelled by the present case law interpreting section 103. Recall that even under the traditional analysis of chemical obviousness, the need for the applicant to present objective evidence of unexpected or non-obvious properties arises only after the Patent Office has established a *prima facie* case of obviousness.[71] In *Papesch*, the *prima facie* case was satisfied by the mere showing of structural similarity between the claimed compound and the prior art compound. Later decisions, however, have held the Patent Office to a higher standard.

For example, in *In re Taborsky*,[72] the court stated that "[i]n determining the propriety of the Patent Office case for prima facie obviousness, it is necessary to ascertain whether the prior art teachings would appear to be sufficient to one of ordinary skill in the art to suggest making the proposed substitution or other modification."[73] More recently, the Court of Appeals for the Federal Circuit has stated that "generaliza-

70. Infringement analysis is discussed *infra* section III. Another alternative is that the parties will agree to cross-license their patents to the other.

71. *In re* Grabiak, 769 F.2d 729, 731 (Fed. Cir. 1985); *In re* Papesch, 315 F.2d 381, 381 (C.C.P.A. 1963).

72. 502 F.2d 775 (C.C.P.A. 1974).

73. *Id.* at 780; *see also In re* Lalu, 747 F.2d 703 (Fed. Cir. 1984).

tion should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other."[74]

The Patent Office Board of Appeals has followed the decisions in this line of cases in deciding the obviousness of a recombinant protein. In *Ex parte Goeddel*,[75] the patent examiner had rejected claims to a recombinant form of human leukocyte interferon which had an amino acid sequence slightly different from that of the naturally occurring interferon, on the grounds that the recombinant protein was structurally obvious and not seen to differ in kind from the natural protein. The Board of Appeals reversed the examiner's rejection, finding that the evidence did not even support a *prima facie* case of obviousness:

> This rejection on its face . . . is not sustainable. The statutory inquiry is obviousness and not "differ in kind." Whatever that means, palpably it is not a proper basis for a rejection. . . . No reasons have been given, nor are apparent to us, which would have motivated the artisan in this field to prepare a "modified" form of the interferons of the prior art by recombinant DNA technology, the isolated natural proteins of the references being limited to those structures and properties as found. That there can be variations in the number of amino acids in natural leukocyte interferons clearly cannot be basis for a holding of obviousness of those at issue, they being neither taught nor suggested by the references, nor present in their systems.[76]

Considered in light of these decisions, a rule of *per se* non-obviousness for novel recombinant protein analogs is not a radical departure from present judicial doctrine, but rather a means for the Patent Office to implement that doctrine in the most efficient manner possible.

## III. INFRINGEMENT OF THE PATENT ON A FIRST-GENERATION RECOMBINANT PROTEIN

There is a high probability that scientists will find some recombinant protein analogs that have new or improved beneficial properties compared to the corresponding first-generation protein.[77] The production of recombinant protein analogs is a worthy pursuit for that reason, and the analogs themselves deserve some degree of patent protection. At the same time, such development efforts clearly pose a competitive threat to the patentee of the first-generation protein. Because the nucleotide sequence disclosure of the gene encoding the first-generation protein enables one of ordinary skill in the art to make analogs, it also

74. *Grabiak*, 769 F.2d at 731.

75. 5 U.S.P.Q.2d 1449 (Bd. Pat. App. & Int. 1985).

76. *Id.* at 1450-51.

77. *See e.g., SmithKline, British Gene Synthesizer Join to Make a 'Third Generation' TPA*, McGraw-Hill's Biotechnology Newswatch, June 1, 1987, at 1; Klausner, *Researchers Probe Second-Generation t-PA*, 4 BIO/TECHNOLOGY 706 (1986).

enables one to attempt to "invent around" the patent on the first-generation protein. This raises a different issue, separate from the question of patentability of recombinant protein analogs, and that is, under what circumstances a second-generation analog will be held to infringe the patent on a first-generation protein.

Under United States law, patent infringement occurs whenever a person "without authority makes, uses or sells any patented invention, within the United States during the term of the patent therefor."[78] Because patent claims measure and define an invention, the first step in analyzing patent infringement is to determine their scope.[79] Claim interpretation is a question of law.[80]

In determining the proper scope of the claims, a court must consider the language of the claims not in isolation, but rather in the context of the patent reference as a whole.[81] Particular attention is given to the specification disclosures, both for meaning of particular terms used in the claims[82] and for an understanding of the invention actually patented. As the Supreme Court has stated, "[w]hile the claims of a patent limit the invention, and specifications cannot be utilized to expand the patent monopoly, it is fundamental that claims are to be construed in the light of the specifications and both are to be read with a view to ascertaining the invention. . . ."[83]

If the alleged infringing matter falls within the scope of the claims as properly construed, there is "literal" infringement.[84] One important way in which the accused infringer may seek to have the court narrowly construe the claims, to avoid a finding of literal infringement, is by raising the enablement requirement of 35 U.S.C. § 112 as a defense.[85] According to section 112, the scope of enablement and the scope of the claims are symmetrical.[86] The relevant inquiry is "whether the scope of

78. 35 U.S.C. § 271(a) (1982).

79. Mannesmann Demag Corp. v. Engineered Metal Products, 793 F.2d 1279, 1282 (Fed. Cir. 1986); Caterpillar Tractor Co. v. Berco, S.P.A., 714 F.2d 1110, 1114 (Fed. Cir. 1983), *cited in* Texas Instruments, Inc. v. United States Int'l Trade Comm'n., 805 F.2d 1558, 1562 (Fed. Cir. 1986). Every patent application must conclude with one or more "claims" particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention. 35 U.S.C. § 112 (1982), para. 2.

80. Johnston v. IVAC Corp., 885 F.2d 1574, 1579-80 (Fed. Cir. 1989).

81. Fonar Corp. v. Johnson & Johnson, 821 F.2d 627, 631 (Fed. Cir. 1987), *cert. denied* 484 U.S. 1027 (1988); Moeller v. Ionetics, Inc., 794 F.2d 653, 656 (Fed. Cir. 1986).

82. *Fonar Corp.*, 821 F.2d at 632; Howes v. Medical Components, Inc., 814 F.2d 638, 644 (Fed. Cir. 1987).

83. United States v. Adams, 383 U.S. 39, 48-49 (1966) (citation omitted).

84. Atlas Powder Co. v. E. I. DuPont de Nemours & Co., 750 F.2d 1569, 1579 (Fed. Cir. 1984).

85. *Id.* at 1576.

86. *In re* Hyatt, 708 F.2d 712, 714 (C.C.P.A. 1983)

enablement provided to one of ordinary skill in the art by the disclosure is such as to be commensurate with the scope of protection sought by the claims."[87]

The question of what analogs are "enabled" for purposes of section 112 by the disclosure of the coding sequence for the first-generation protein is related to the question of what analogs are rendered obvious for purposes of section 103.[88] The predictability of an analog's functional properties helps in determining whether the analog is enabled by the patent on a first-generation protein in the same way that it helps in determining whether the analog is obvious.

In the chemical arts, the relationship between the predictability of the subject matter claimed and the scope of enablement is illustrated by the case of *In re Fisher*.[89] In *Fisher*, the applicant claimed as his invention preparations of the natural protein, adrenocorticotrophic hormone (ACTH), having a potency of "at least 1 International Unit of ACTH per milligram." The specification disclosed a method of producing ACTH preparations having potencies of 1.11 to 2.3 International Units per milligram.[90] The issue was whether the disclosure of preparations of ACTH of rather limited potency could support the claim to all preparations having a potency of greater than one International Unit per milligram, including future preparations having potencies far in excess of those disclosed. The court said "no," holding that the scope of enablement provided by the specification was limited by the unpredictable nature of the scientific methods involved:

> [Section 112] requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.[91]

87. *In re* Moore, 439 F.2d 1232, 1236 (C.C.P.A. 1971); *see also Hyatt*, 708 F.2d at 715.

88. For a general discussion of the relationship between obviousness and enablement, see D. Chisum, *Anticipation, Enablement and Obviousness: An Eternal Golden Braid*, 15 AIPLA Q. J. 57 (1987).

89. 427 F.2d 833 (C.C.P.A. 1970).

90. *Id.* at 834-35.

91. *Id.* at 839.

Similarly, inventions based on recombinant DNA technology generally involve unpredictable factors and thus enable a narrower range of claims.[92]

That, however, does not necessarily mean that the claims in a patent on a first-generation recombinant protein must be limited to cover only that protein. The claims may extend to analogs of the first-generation protein, notwithstanding the general unpredictability of the technology involved, provided that the disclosures in the patent are complete enough to enable one of ordinary skill in the art to make and use the claimed analogs without "undue experimentation."[93]

What constitutes undue experimentation is not a simple factual determination. Rather, it is a conclusion reached by weighing several factors, including the quantity of experimentation necessary, the amount of direction or guidance provided by the disclosures in the patent, and the presence or absence of working examples.[94] In the recent case of *In re Mark*,[95] the U.S. Patent Office Board of Appeals dealt specifically with this issue in the context of recombinant protein analogs.

In *Mark*, the appealed claims were directed to all analogs ("muteins") of all biologically active native proteins, which analogs have the same biological activity and the same amino acid sequence as the corresponding native protein except that a single amino acid, cysteine, that is present in the native protein is deleted or substituted by a different amino acid in the analog. The patent examiner rejected those claims under 35 U.S.C. § 112, first paragraph, for lack of a sufficiently enabling disclosure. The specification disclosed the preparation, by recombinant methods, of cysteine-mutant analogs of three different native proteins, interferon-beta, interleukin-2, and tumor necrosis factor. Essentially, the position taken by the examiner was that it would require undue further experimentation to construct the innumerable analogs encompassed by the claims and to screen the analogs produced for any of those which retained biological activity.

The Board of Patent Appeals, however, held that the claims were enabled and reversed the examiner's rejection. Of apparent importance to the Board were the facts that the claimed analogs were limited to those having a certain biological property, and that the application dis-

92. Hormone Research Found. v. Genentech, Inc., 708 F. Supp. 1096, 1108 (N.D. Cal. 1988); *Ex parte* Forman 230 U.S.P.Q. 546, 548 (Bd. Pat. App. & Int. 1986).

93. *See, e.g.*, Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986), *cert. denied* 480 U.S. 947 (1987); *In re* Angstadt, 537 F.2d 498, 504 (C.C.P.A. 1976).

94. *In re* Wands, 858 F.2d 731, 737 (Fed. Cir. 1988); *Forman*, 230 U.S.P.Q. at 547.

95. 1989 Pat. App. LEXIS 12 (Bd. Pat. App. & Int. 1989).

closed routine methods by which such analogs could be prepared and identified:

> When it is considered that the claims remaining on appeal all require that the mutein produced retain the biological activity of the native protein, we consider the disclosure of this application to be enabling. . . . The record before us establishes that for a given protein having cysteine residues, one skilled in the art would be able to routinely determine whether deletion or replacement of the cysteine residues would result in a mutein which is within the claims on appeal.[96]

It remains to be seen how this decision will be applied in determining the scope of permissible claims in a patent on a first-generation recombinant protein. At the very least, *Mark* suggests that the claims should be limited to encompass only those analogs having certain well-defined functional properties—specifically, the same properties as the first-generation protein. Absent working examples of analogs having functional properties different from the first-generation protein, claims encompassing such analogs should be rejected for lack of enablement, on the grounds that their existence is wholly unpredictable.

If a second-generation analog does not literally infringe the patent on a first-generation recombinant protein, it still may be found to infringe under the "doctrine of equivalents."[97] Under this judicially-created doctrine, a product that does not fall within the literal language of the patent claims, but does perform "substantially the same overall function or work, in substantially the same way, to obtain substantially the same overall result as the claimed invention,"[98] will infringe that patent. The doctrine's purpose is equitable. It protects the patentee from the "unscrupulous copyist . . . [who makes] unimportant and insubstantial changes and substitutions in the patent which, though adding nothing, would be enough to take the copied matter outside the claim, and hence outside the reach of the law."[99]

In applying the doctrine of equivalents, the degree of protection afforded beyond the language of the claims will vary directly with the value of the inventor's contribution to the art.[100] Where the court is confronted with a so-called "pioneer" invention,[101] "liberality becomes

96. *Id.* at *9.

97. *See, e.g.*, Hughes Aircraft Co. v. United States, 717 F.2d 1351, 1361 (Fed. Cir. 1983).

98. Pennwalt Corp. v. Durand-Wayland Inc., 833 F.2d 931, 934 (Fed. Cir. 1987), *cert. denied* 485 U.S. 961 (1988).

99. Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 607 (1950).

100. *See* Texas Instruments, Inc. v. U.S. Int'l Trade Comm'n., 846 F.2d 1369, 1370 (Fed. Cir. 1988).

101. Westinghouse v. Boyden Power Brake Co., 170 U.S. 537, 562 (1898) (Pioneer inventions are "a distinct step in the progress of the art, distinguished from a mere improvement or perfection of what had gone before").

the keynote of construction requiring the court to give the patentee a wide breadth of protection in construing the patent claims and specifications."[102]

Relying on these two approaches to infringement, what can be said about the scope of protection afforded by the patent on a first-generation recombinant protein? The patent on the first-generation protein at least encompasses those analogs with properties similar in type and degree to the first-generation protein, as long as they are specifically claimed and can be prepared without undue experimentation. Even if not within the literal claim language, such analogs would likely infringe under the doctrine of equivalents. In *Hybritech v. Abbott Laboratories*, for example, the district court held that the use of antibody "Fab" fragments — essentially, truncated forms of native antibody proteins — in an antigen-binding assay infringed, under the doctrine of equivalents, claims directed to the use of whole antibodies in such an assay, on the grounds that Fab fragments "do the same thing in essentially the same way as the whole antibody."[103]

The difficult question is where to draw the line when the analog has properties which differ in degree from the first-generation protein. For example, would an analog with 10% greater biological or therapeutic activity be held to infringe under the doctrine of equivalents on the grounds that it is "substantially" the same as the first-generation protein? What about an analog with 50% or 100% greater activity?

One possible answer to the line-drawing question may be found in *Atlas Powder Co. v. E. I. DuPont de Nemours & Co.*[104] In that case, the Court of Appeals for the Federal Circuit suggested in dicta that the granting of a patent on a product "A" may be evidence of non-infringement under the doctrine of equivalents of the patent on product "B," provided that product "A" was patented on the basis of certain unexpected properties not present in product "B." The court reasoned that a finding of non-equivalence would be proper in such a case because the two products would achieve substantially different results, in contravention of the third prong of the doctrine of equivalents test.[105] According to this view, an analog that a patent examiner determines has properties sufficiently different in degree to be found non-obvious, would also be non-equivalent and, thus, non-infringing.

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102. Corning Glass Works v. Anchor Hocking Glass Corp., 374 F.2d 473, 476 (3d Cir. 1967), *cert. denied* 389 U.S. 826 (1967).

103. 4 U.S.P.Q.2d 1001, 1012 (C.D. Cal. 1987), *aff'd* 849 F.2d 1446 (Fed. Cir. 1988).

104. 750 F.2d 1569 (Fed. Cir. 1984).

105. *Id.* at 1580 n.3.

Analogs with properties different *in kind* from the first-generation protein are not likely to infringe the first patent. Claims which literally encompass analogs with differing properties should not be allowed by an examiner. Nor would such an analog be found to infringe under the doctrine of equivalents. As stated in *Papesch*, "from the standpoint of patent law, a compound and all of its properties are inseparable."[106] The invention embodied by the patent on a first-generation protein is not merely the protein structure or the particular sequence of amino acids, rather, the invention is the protein as a whole, comprising a sequence of amino acids and possessing certain defined properties. Accordingly, analogs with properties altogether different from those of the corresponding first-generation protein should certainly be considered outside the scope of that invention.

## IV. CONCLUSION

The U.S. Patent Office and the courts share responsibility for assuring that the inventors of first- and second-generation recombinant proteins receive adequate protection for their inventions under existing patent laws.

The Patent Office should adopt reasonable procedures for determining the patentability of second-generation recombinant proteins to expedite the issuance of patents for products legitimately deserving of protection. One step in that direction would be for the Patent Office to adopt a *per se* rule of non-obviousness for second-generation recombinant proteins until further advances in the art make the prediction of some protein structure-to-function relationships possible.

The claims allowed for the patent on the first-generation protein should be broad enough to cover the invention actually enabled by the disclosure, but nothing more. In construing those claims, courts should accord protection commensurate in scope with the inventor's contribution to the public. In view of the ease with which competitors can make analogs once a protein's nucleotide sequence is revealed, the original patent claims should be construed to include those analogs where the changes are insignificant. Absent that, the patent on a first-generation protein will be little more than an invitation for others to appropriate the invention by making minor modifications to the protein.

At the same time, however, the Patent Office and courts must not give the inventor of the first-generation protein complete control over all subsequent advances and developments which may derive from the patent disclosure. Although the task of balancing the competing interests

106. *In re* Papesch, 315 F.2d 381, 391 (C.C.P.A. 1963).

of the patentee and the public may be difficult, no less is required if the patent system is to remain a viable incentive to innovation in this area of biotechnology.

APPENDIX A

## SUMMARY OF PENDING BIOTECHNOLOGY PATENT LITIGATION

| Plaintiff | Defendant | Product | Action |
|---|---|---|---|
| Amgen | Genetics Institute | erythropoietin | Both parties' patents held valid and infringed. Parties have begun cross-licensing discussions. |
| BioPolymers | Genex | mussel-glue | Suit settled February 1989. BioPolymers will grant Genex a non-exclusive license to its patent. |
| Eli Lilly | Genentech | human growth hormone | Suit filed in U.S. District Court in March 1987 alleging invalidity of four patents. As patents issue worldwide, Lilly initiates suits (England, France, New Zealand, and South Korea). |
| Genentech | Wellcome Foundation | tPA | Genentech's U.K. patent held invalid as being overly broad. |
| Genentech | Toyobo | tPA | Suit filed in Japan in August 1987, alleging infringement of Genentech's Japanese patent. Genentech's motion for temporary injunction denied. |
| Genentech | Abbott | tPA | Suit filed April 1988, seeking declaratory judgment of invalidity or non-infringement. |
| Hoffman-La Roche | Wellcome | alpha-interferon | Suit filed October 1986, alleging infringement of Hoffman-La Roche patent. |
| Hormone Research | Genentech | human growth hormone | Suit filed alleging infringement of Hormone Research patent. |
| Scripps | Genentech | Factor VIII | Scripps won summary judgment on infringement suit in 1987. Scripps patent held invalid in 1989. |

## APPENDIX B
## EXAMPLE OF PATENT CLAIM DIRECTED TO SECOND-GENERATION RECOMBINANT PROTEIN ANALOGS

What is claimed is:

1. A polypeptide having an amino acid sequence represented by formula [I] below in which at least one of the 16th, 31st to 34th, 36th, 48th, 73rd, 82nd, 85th, 89th, 94th, 97th, 98th, 103rd, 113th, 115th, 117th, 118th, 131st, 132nd, 141st to 146th, and 153rd amino acid residues is replaced by another amino acid residue, with the proviso that when the 115th amino acid residue is replaced by another amino acid residue, the 67th amino acid residue and/or the 99th amino acid residue may be replaced by another amino aid residue; or a polypeptide resulting from deletion of one or at most 8 successive amino acid residues from the N-terminus of said polypeptide:

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Ser | Ser | Ser | Arg | Thr | Pro | Ser | Asp | Lys | Pro |
| Val | Ala | His | Val | Val | Ala | Asn | Pro | Gln | Ala |
| Glu | Gly | Gln | Leu | Gln | Trp | Leu | Asn | Arg | Arg |
| Ala | Asn | Ala | Leu | Leu | Ala | Asn | Gly | Val | Glu |
| Leu | Arg | Asp | Asn | Gln | Leu | Val | Val | Pro | Ser |
| Glu | Gly | Leu | Tyr | Leu | Ile | Tyr | Ser | Gln | Val |
| Leu | Phe | Lys | Gly | Gln | Gly | Cys | Pro | Ser | Thr |
| His | Val | Leu | Leu | Thr | His | Thr | Ile | Ser | Arg |
| Ile | Ala | Val | Ser | Tyr | Gln | Thr | Lys | Val | Asn |
| Leu | Leu | Ser | Ala | Ile | Lys | Ser | Pro | Cys | Gln |
| Arg | Glu | Thr | Pro | Glu | Gly | Ala | Glu | Ala | Lys |
| Pro | Trp | Tyr | Glu | Pro | Ile | Tyr | Leu | Gly | Gly |
| Val | Phe | Gln | Leu | Glu | Lys | Gly | Asp | Arg | Leu |
| Ser | Ala | Glu | Ile | Asn | Arg | Pro | Asp | Tyr | Leu |
| Asp | Phe | Ala | Glu | Ser | Gly | Gln | Val | Tyr | Phe |
| Gly | Ile | Ile | Ala | Leu | | | | . . . | [I] |

2. A polypeptide according to claim 1 wherein
(A) at least one of the following replacements of amino acids in the amino acid sequence of formula [I] is effected:

| | | |
|---|---|---|
| 16th | Ala | by Val, |
| 31st | Ala | by Thr, |
| 32nd | Asn | by Ala, Cys, Asp, His, Ile, Arg, Ser, Thr, Val, or Tyr, |

| | | |
|---|---|---|
| 34th | Leu | by Ile, |
| 36th | Ala | by Val, |
| 48th | Val | by Met, |
| 73rd | Leu | by Pro, |
| 82nd | Ala | by Asp, |
| 85th | Tyr | by His, |
| 89th | Val | by Ile, |
| 94th | Ala | by Thr, |
| 97th | Ser | by Asn, |
| 98th | Pro | by His or Leu, |
| 103rd | Thr | by Pro, |
| 113th | Tyr | by Cys, |
| 115th | Pro | by Leu, His, Gln, Ser, Ala, Phe, Asn, Gly, Tyr, Val, Glu, Met, Ile, Asp, Trp, Lys, Arg, or Thr, |
| 117th | Tyr | by His, |
| 118th | Leu | by Gln, |
| 131st | Ser | by Ile, |
| 132nd | Ala | by Thr, |
| 141st | Asp | by Tyr, |
| 143rd | Ala | by Val, |
| 144th | Glu | by Lys, |
| 145th | Ser | by Cys, |
| 146th | Gly | by Glu, and |
| 153rd | Ile | by Leu; |

(B) 67th Cys and/or 99th Cys are replaced by Ser and 115th Pro is replaced by an amino acid other than Pro in an amino acid sequence represented by formula [I]; or
(C) the polypeptide (A) or (B) in which one or at most 8 successive amino acid residues from the N-terminus is deleted.