

COMMENT

PROTEIN PATENTS AND THE DOCTRINE OF EQUIVALENTS: LIMITS ON THE EXPANSION OF PATENT RIGHTS

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I. INTRODUCTION

A little over a decade ago, the Supreme Court in *Diamond v. Chakrabarty*¹ held that inventions involving living organisms altered by man were entitled to patent law protection. The Court's interpretation of the breadth of section 101 of the Patent Act² provided the nascent biotechnology industry with precisely the type of stimulus necessary to launch and drive a furious and exciting period of development. The phenomenal volume of patent application filings which followed the Court's holding, as well as the vigorous enforcement postures assumed by biotechnology firms over the past decade, illustrate the importance biotechnology companies place on patent protection. The industry's reactions to *Chakrabarty* also demonstrate the capacity of an effective patent system to drive innovation and development, as well as encourage investment.³

Developers of blockbuster drugs, such as erythropoietin, tissue plasminogen activator, and factor VIII:c, are now beginning to realize the rewards made possible through the exercise of effective patent rights. For example, the recent holding of the Federal Circuit in *Amgen, Inc., v. Chugai Pharmaceutical Co.*⁴ had the effect of giving Amgen exclusive rights to the recombinant manufacture and sale of the anemia drug erythropoietin in the United States. In response to this holding, Amgen's stock jumped nearly 20% overnight while the stock of Genetics Institute, a co-defendant in the case, declined by nearly a third. The events surrounding the *Amgen* decision demonstrate the value of strong and enforceable patent rights, as well as the importance of adequately and effectively defining rights to the products of biotechnology through patents.⁵

1. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

2. 35 U.S.C. § 101 (1988).

3. In the research-intensive biotechnology industry, patents serve three essential functions. First, patents help inventors protect the long term commitments required for investigation and development of unknown, and unproven areas of biochemistry and molecular biology. Second, patents provide the sponsors of such efforts a means for protecting their often substantial investments. Finally, the active scientific community gains immeasurably by the early disclosure of both important and incremental scientific advances. For start-up biotechnology ventures and established pharmaceutical firms alike, these functions of the patent system have proven to be not only desirable, but essential. See The Report of the President's Commission on the Patent System, November 17, 1966. See generally R. CHOATE, W. FRANCIS & R. COLLINS, PATENT LAW 70-75 (1987).

4. 927 F.2d 1200 (Fed. Cir. 1991). The holding invalidated certain patent claims to naturally derived erythropoietin held by Genetics Institute due to deficiencies under 35 U.S.C. § 112, and affirmed the validity of most of Amgen's host cell and native sequence DNA patent claims.

5. Just 4 days before the Federal Circuit handed down its decision in *Amgen*, one biotechnology stock analyst had even gone to the point of classifying Amgen stock as "sell," Amgen stock rose \$12 per share the day after the decision was made public. See Fisher, *Still More Growth in Biotechnology?*, N.Y. Times, March 1, 1991, at 8.

Effective enforcement of one's patent rights depends on the underlying patent application, the patent claims, and the prosecution history. Inadequacies in any of these three elements can effectively negate the patent as a viable safeguard of investments in time, money, and research. Of the three elements, the claims are the most important for purposes of assessing the scope of enforceable rights possessed by a patentee. Inadequacies in the claim scope are thus immediately thrust to the forefront, and can become a serious stumbling block for the patentee attempting to enforce its rights. In view of the important role claims play in the interpretation and effective use of patent rights, this paper will focus on how claims function to protect inventions in the field of biotechnology, and in particular, will explore the options available to the patentee once the literal scope of the patent claims to a new and useful genetically engineered-protein proves inadequate.

Consider a situation where a broad, yet poorly drawn patent claim is invalidated due to formalistic deficiencies, leaving the patentee with a scope of protection not much broader than the actual species of protein developed.⁶ When this occurs, or when the patentee holds an original claim so limited, the patentee finds itself exposed to the threats of competitors who can easily make insignificant changes and escape the literal scope of the claims.⁷ To permit a third party to easily evade the literal scope of a protein patent claim, and exploit the often significant efforts and costs incurred by a patentee in identifying, isolating, and effectively producing a protein, seems unjust. Yet, the Federal Circuit has emphasized that the function of the claims are to measure the enforceable scope of patent protection and that this function must be preserved in order to ensure that patents continue to stimulate further innovation.⁸ A

6. Reference is made here to claim 7 of the Amgen patent. The claim literally encompassed DNA which encoded any form or derivative of erythropoietin which had a structure similar enough to the native structure so as to allow possession of the same biological activity as native erythropoietin. The lower court's holding of invalidity of this claim due to lack of enablement was affirmed by the Federal Circuit, albeit through a different rationale. The suite of patent claims Amgen retained was thus limited to DNA which encoded, and host cells which expressed native sequence erythropoietin, a scope of protection significantly less than that afforded by the original patent. *Amgen*, 927 F.2d at 1212-13.

7. Literal infringement only occurs when an accused device possesses all the limitations found in a claim. Thus, literal enforcement of a protein sequence claim provides the patentee with an extremely narrow enforceable scope of protection; namely, to the precise amino acid sequence listed in the claim or possessed by the protein.

8. As the Federal Circuit noted in *Perkin-Elmer Corp. v. Westinghouse Electric Corp.*, 822 F.2d 1528, 1532 (Fed. Cir. 1984),

Though the doctrine of equivalents is designed to do equity, and to relieve an inventor from a semantic strait jacket when equity requires, it is not designed to permit wholesale redrafting of a claim to cover non-equivalent devices, i.e., to permit a claim expansion that would encompass more than an insubstantial change.

Recently, the Federal Circuit again emphasized that the right of the public to "design around" the claims of a patent is an inherent, and absolutely essential element of the

court presented with this type of dilemma of resolving the relative rights of the patentee and the alleged infringer must act within an equitable framework.

The doctrine of equivalents⁹ provides such an equitable framework.¹⁰ It seems appropriate that a patentee holding unduly narrowed patent claims to a protein should be able to bypass the restrictions imposed by the literal scope of patent claims in extraordinary situations to protect him 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 law."¹¹ Indeed, the analysis of this issue by the Federal Circuit in its opinion in *Hormone*

United States patent system. In *Slimfold Mfg. Co., Inc., v. Kinkead Indus., Inc.*, 932 F.2d 1453, 1457 (Fed. Cir. 1991), the court held:

Intentional "designing around" the claims of a patent is not by itself a wrong which must be compensated by invocation of the doctrine of equivalents. Designing around patents is, in fact, one of the ways in which the patent system works to the advantage of the public in promoting progress in the useful arts, its constitutional purpose. Inherent in our claim-based patent system is also the principle that the protected invention is what the claims say it is, and thus that infringement can be avoided by avoiding the language of the claims.

9. Under the doctrine of equivalents, a device infringes "if it performs substantially the same function in substantially the same way, to obtain substantially the same result." *Graver Tank & Mfg. Co., v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950), *reh'g denied*, 340 U.S. 845 (1950). The doctrine is founded on the theory that "if two devices do the same work in substantially the same way, and accomplish substantially the same result, they are the same, even though they differ in name, form or shape." *Id.*

10. The Federal Circuit has repeatedly stressed that there is an equitable basis for the doctrine, and that this basis must be considered when applying the doctrine of equivalents. *See, e.g.,* *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 870 (Fed. Cir. 1985) ("The doctrine [of equivalents] has been 'judicially devised to do equity' in situations where there is no literal infringement but liability is nevertheless appropriate to prevent what is in essence a pirating of the patentee's invention."). The rationale of the doctrine was perhaps best stated in *Texas Instruments, Inc., v. I.T.C.*:

The doctrine of equivalents, ubiquitous since its origin in *Winans v. Denmead*, 56 U.S. (15 How.) 330 (1853), exists solely for the equitable purpose of "prevent[ing] an infringer from stealing the benefit of an invention." *Graver Tank*, 339 U.S. at 608. To achieve this purpose, equivalency is judicially determined by reviewing the content of the patent, the prior art, and the accused device, and essentially redefining the scope of the claims. This constitutes a deviation from the need of the public to know the precise legal limits of patent protection without recourse to judicial ruling. For the occasional pioneering invention, devoid of significant prior art—as in the case before us—whose boundaries probe the policy behind the law, there are no immutable rules. We caution that the incentive to innovation that flows from "inventing around" an adversely held patent must be preserved. To the extent that the doctrine of equivalents represents an exception to the requirement that the claims define the metes and bounds of the patent protection, we hearken to the wisdom of the Court in *Graver Tank*, that the purpose of the rule is "to temper unsparing logic" and thus to serve the greater interest of justice.

805 F.2d 1558, 1583 (Fed. Cir. 1986).

A good overview of the equitable origin of the doctrine of equivalents is found in H. WEGNER, *EQUITABLE EQUIVALENTS: WEIGHING THE EQUITIES TO DETERMINE PATENT INFRINGEMENT IN BIOTECHNOLOGY AND OTHER EMERGING TECHNOLOGIES* (1991).

11. *Graver Tank*, 339 U.S. at 607.

*Research Foundation v. Genentech*¹² indicates that the *equitable* doctrine of equivalents does have a role to play in enforcement of protein claims.

Application of the doctrine to actions for infringement of protein patent claims must be approached carefully by the court when it weighs the equities of the case before it. For example, few would hesitate to label a "conservative" amino acid substitution¹³ in a polypeptide sequence of a complex, patented protein, which was implemented for the sole purpose of escaping the literal scope of a patent claim, as anything but an "unimportant and insubstantial" modification.¹⁴ Allowing the patentee to expand the enforceable scope of protection of a patent claim without restriction, however, seems inequitable to later parties who do not derive their work from that of the patentee, especially where a modified protein is superior to the earlier, patented protein.¹⁵ A third, often overlooked

12. 904 F.2d 1558 (Fed. Cir. 1990). The Federal Circuit reversed the lower court's holding on summary judgment that statements of the inventor created a prosecution history estoppel and barred the application of the doctrine of equivalents, and remanded the case to ascertain whether the statements, in fact, did create an estoppel. *Id.* at 1569. In the course of doing this the court referred to the equitable nature and origin of the doctrine of equivalents. *Id.* at 1564.

13. A "conservative" amino acid substitution is one which does not affect the structure or function of a polypeptide. Most often, a conservative change is limited to a substitution in the amino acid sequence of a single amino acid which shares the physico-chemical attributes of the amino acid which is replaced. Such a change escapes literal infringement of a patent claim to the native sequence protein simply because the changed protein is now chemically distinct from the native sequence protein. For example, a claim limited to a protein which includes the sequence "X-Gly-Ser-Glu-Y" would not be infringed by a protein having the sequence "X-Gly-Ser-Asp-Y" as the latter protein is a distinct chemical entity from the claimed protein. For those readers unfamiliar with protein technology, a brief summary is provided *infra* p. 113.

14. As the Supreme Court stated in the seminal case on the doctrine of equivalents, "[t]o permit imitation of a patented invention which does not copy every literal detail would be to convert the protection of the patent grant into a hollow and useless thing." *Graver Tank*, 339 U.S. at 607.

15. The Federal Circuit, in its opinion in *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991), left open the question of whether patent rights from a claim based upon purification from natural sources would dominate later claims to a slightly different recombinant version of the same protein. The direct question of construction of the naturally derived protein claim to incorporate the process by which it was produced was avoided due to inconsistent legal arguments presented by Genentech. The related question of whether the "reverse doctrine of equivalents" should apply to limit the enforceable scope of a claim which could be construed to literally read upon the later product was remanded to the district court, pursuant to a reversal of a summary judgment finding of no infringement. *Id.* at 1580-81. As to this point, the court stated:

Genentech asserts that the specific activities and purity that are obtainable by recombinant technology exceed those available by the Scripps process; an assertion disputed by Scripps, but which if found to be correct could provide—depending on the specific facts of similarities and differences—sufficient ground for invoking the reverse doctrine.

Id. at 1581.

Later in the decision, the court addressed the question raised by Scripps as to whether a claim to a protein phrased in product-by-process format could resort to the doctrine of equivalents to support a finding of infringement against a substantially identical form of

factor should also be taken into account: namely, the dubious societal value of an overly expansive doctrine of equivalents.¹⁶ When courts allow the doctrine of equivalents to serve as an easily invoked and loosely applied adjunct to literal infringement, they create a risk of muddying the already murky waters of protein patent claim interpretation.

These equitable considerations have been the primary focus of doctrine of equivalents analysis since its inception. The mechanics of doctrine of equivalents analysis, however, have been refined substantially in recent years. This is largely attributable to the creation of the Court of Appeals for the Federal Circuit.¹⁷ For example, a patentee in today's court who seeks to use the doctrine of equivalents now faces not only the burden of proving actual equivalence, but also the burden of proving that the expanded scope of protection sought will not ensnare the prior art in existence at the time of the patent grant. This second burden has, until recently, been largely ignored, or left for either the court or the defendant to the infringement action to raise. Last year, the Federal Circuit, in *Wilson Sporting Goods, Inc. v. David Geoffrey Associates*,¹⁸ explained this new burden of proof and indicated the proper role that the doctrine of equivalents should have in the enforcement of patent claims.¹⁹ As protein technology matures and the emphasis of innovation shifts from newly discovered proteins to modified and "improved" variants, the doctrine of equivalents will play an increasingly important role in the enforcement of protein patents. This paper attempts to provide the reader with a perspective on some of the issues facing a patentee contemplating such use of the doctrine of equivalents.

the protein produced using recombinant techniques. *Id.* at 1583-84. Here the issue was whether the naturally derived factor VIII:C protein, phrased in the product-by-process claim format could reach the recombinantly derived factor VIII:C protein produced by Genentech. In remanding the case to the district court for assessment of the claim of infringement of the product-by-process claims, the court held that

[i]n determining patentability we construe the product as not limited by the process stated in the claims. Since claims must be construed the same way for validity and for infringement, the correct reading of product-by-process claims is that they are not limited to product prepared by the process set forth in the claims.

Id. at 1583. Instead, the court held that the product claims must be construed for purposes of infringement pursuant to standards applicable to regular product claims not possessing process limitations. *Id.*

16. Indeed, one may question whether a pro-innovation patent policy is actually served at all by provision of an expansive doctrine of equivalents. Such a policy can create confusion as to patent rights, both for the patentee and for parties pursuing products outside the literal scope of a patentee's claims. It may also render a reward far in excess of the original contribution of the patentee through a process wholly removed from the arguably balanced patentability analysis conducted by the Patent and Trademark Office. Uncertainty over the basic question of infringement may even serve to discourage investment and research. See Merges & Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839 (1990).

17. Federal Courts Improvement Act of 1982, 28 U.S.C. § 1295 (1988).

18. 904 F.2d 677 (Fed. Cir. 1990), *cert. denied*, 111 S. Ct 537 (1990).

19. See *infra* note 58 for discussion.

II. OVERVIEW OF PROTEIN TECHNOLOGY

The initial goal of many biotechnology companies during the 1980's was the exploitation of a known, pharmaceutically important protein. This goal seemed both attractive and attainable due to the advances in genetic engineering which were being taking place. For example, through the exercise of relatively straight forward laboratory procedures, a researcher could transform the genetic makeup of a host cell thereby inducing that cell to produce a desired protein. This process of exploiting nature's own resources could thus be used to simultaneously solve the problems of purity and quantity which prevented earlier exploitation of the protein through conventional purification technology.

This initial objective and accomplishment of many biotechnology firms pales in comparison to the potential of applied protein engineering. The ability of a protein engineer to dissect and reassemble segments of biologically active proteins to arrive at completely new and useful proteins holds incredible potential.²⁰ Native proteins thus may become "building blocks" for an entirely new generation of protein entities. With these technological advances, new legal questions have arisen. In the context of defining patent rights, the most important question is what impact will the grant of initial patents covering native proteins have on the patenting and production of these "third generation" products?

A. Fundamental Principles and Terms of the Art

Some proteins are commercially interesting compounds because they possess a desirable biological activity. Examples of such proteins are tissue plasminogen activator (t-PA), which breaks down blood clots, and erythropoietin (EPO), which stimulates the production of red blood cells. The relationship between a protein's biological activity and its structure, however, is rarely, if ever completely understood. However, it is this relationship between structure and function which is most critical for the predictive use of protein structure information to engineer new protein analogs which retain or introduce desired biological functions of known proteins.

A brief overview of the fundamentals of protein structure and function may be helpful at this point. Proteins are complex macromolecular chemical structures, composed of one or more polypeptide chains. Each polypeptide is made up of a linear sequence of amino acid residues covalently attached to each other through peptide

20. For example, using recombinant techniques, a protein engineer can assemble a hybrid protein having the regions of an antibody which give the antibody its unique specificity, and the cell killing potential of a highly lethal toxin, yielding a safe "magic bullet" that can selectively find and kill cancer cells. See, e.g., Merz, *Fine-tuned and Loaded, Monoclonals Treat Cancer*, 256 J. A.M.A. 1406, 1412 (1986).

bonds.²¹ This linear amino acid sequence is termed the primary structure of a protein. There are only 20 commonly occurring amino acids. However, this small number is sufficient to yield an enormous number of possible polypeptide sequences.²² These polypeptide sequences possess a dramatic range of physico-chemical properties, which impart an almost incomprehensible range of possible protein structures and biological activities.

Each amino acid residue in a protein sequence plays a different role in defining the overall structure of a protein, depending on the nature of the side chain group which is attached to the central or alpha carbon. The chemical nature of the side chain group defines whether the amino acid residue will impart a hydrophilic ("water loving") or hydrophobic ("water hating") effect upon the region of the polypeptide chain in which the residue is located.²³ The localized effect of different interactions between adjacent amino acid side chains, in combination with the restricted rotational flexibility of the basic polypeptide chain,²⁴ gives rise to a limited number of energetically favored localized conformations. These conformations are termed the secondary structure of the protein.²⁵

The secondary structure plays an important role in how the protein assumes its overall three dimensional conformation, termed the tertiary structure of the protein. A protein has a quaternary structure if more than one polypeptide chain contributes to its conformation. Individual polypeptide chains can assume, in theory, a tremendously large number of possible overall conformations.²⁶ In nature they typically assume only

21. The peptide bond is represented as follows: $R(NH)(CO)CHX-R$, where R represents strings of amino acids, and X represents the side chain group of the central amino acid depicted.

22. Depending upon the length of the polypeptide chain, an incredibly large number of possible distinct or unique polypeptide entities can be imagined. For example, a polypeptide chain having 100 sequential amino acid residues can give rise, in theory, to 20^{100} possible sequences.

23. Residues having a nonpolar, uncharged side group impart hydrophobic effects (e.g. Ala, Val, Leu, Ile, Pro, Met, Phe, Trp). Residues which are polar and either charged or uncharged impart hydrophilic effects (e.g. Gly, Ser, Thr, Cys, Tyr, Asp, Glu, Asn, Gln, Lys, Arg, His). See LEHNINGER, *BIOCHEMISTRY* 100-03 (1982).

24. The peptide bond has a "double bond-like" character, forcing it to adopt a planar conformation. The combined effect of this "rigid" structure and the interactions between the side chains attached to the alpha-carbon has a significant influence upon the secondary structure of the peptide region. See *id.* at 150-52.

25. Early studies focused on two predominant conformations for secondary structures: the alpha helix and the β -pleated sheet. The former resembles a repeating spring-like or twisted rope-like coil structure, while the latter is an extended or "stretched" conformation. See *id.* at 151-56. Due to more complex molecular modeling systems and increased information from X-ray diffraction studies, additional conformations, such as tight turns, small loops, and random coils, have been deduced, and more accurate estimates of the regional conformations of proteins can therefore be made.

26. The hypothetical 100 residue polypeptide could assume 10^{100} "energetically reasonable" conformations. T. CREIGHTON, *PROTEINS* 135 (1984).

a few preferred, or native conformations. These conformations are normally the most stable, or lowest energy, forms of the protein, taking into account all the possible interactions between different regions or domains of the protein²⁷ and between the protein and its local environment. Typically, the preferred conformations are the ones in which a protein exhibits its biological activity. For the protein chemist, attempting to "engineer" a novel, biologically active form of a protein, conformations therefore become extremely important.

B. Understanding the Importance of Protein Conformations

As noted earlier, biologically active proteins are often extremely complex chemical structures. This complexity is due primarily to the way proteins change or adopt conformations in response to different physiological conditions.²⁸ These conformations are influenced by a bewildering array of interrelated forces, each having a variable degree of impact on the overall conformation of the protein. More than anything else, the extremely complex interrelationship between structure, conformation, and biological activity renders protein "engineering" an inherently unpredictable and imprecise discipline. While a complete summary of all the possible forces which influence a protein's conformational dynamics is beyond the scope of this paper, one can get a feel for the difficulty associated with the prediction of such conformations by recognizing the major factors which influence protein conformations.

The primary structure of a protein is the most direct influence on the overall conformation and activity of a protein, simply because it serves to define the various secondary, tertiary, and quaternary structures possessed by a protein. The primary structure of a protein is also the one structure protein engineers have which can be directly measured, which will remain static, and which must be used to base conclusions and make predictions. Thus, the amino acid sequence of the protein often becomes the primary focus when studying a protein's conformational dynamics and their effects upon biological activity and function.

Regions of secondary structures, on the other hand, play a dynamic role in defining which of the many possible conformations the protein will assume at any one time. First, different regions of secondary

27. Regions or domains as used here means those identifiable stretches of amino acids having distinct secondary structures.

28. Most biologically active proteins have three-dimensional conformations which are "globular," meaning their conformations are composed of many secondary structures. On the other hand, structural proteins which make up things like muscle and hair are "ordered" structures in the sense that they have identifiable, repeating, and predictable conformations. A globular protein does not have a fixed and readily predictable structure. Instead, these proteins are loosely ordered and frequently shift between many different overall conformations.

structures can interact with each other. For example, hydrophobic regions will often associate in pockets within the protein because less energy is required for them to interact with each other than to interact with the aqueous environment.²⁹ Conversely, hydrophilic regions are readily soluble in an aqueous environment and tend to reside on the outer regions of the protein which are exposed to the aqueous environment. The combined effect of these region-to-region interactions plays a large role in defining the predominant tertiary conformation of the protein, and therefore, its overall three-dimensional conformation.

Where a protein is actually a complex of several distinct polypeptide chains, interactions analogous to intra-chain interactions occur. Instead of two regions from a single polypeptide interacting with each other, regions in distinct polypeptides interact. There is a much greater range of variability in the overall conformations possible in these types of interactions because the involved regions are not necessarily constrained by being on the same chain.

If the sole source of influence for conformational changes in a protein were its amino acid sequence, predictions of protein conformations would still remain complex and largely empirical. This, however, is not the case. Many factors other than the amino acid sequence of the protein serve to influence and change its conformations. First, the physical environment in which the protein exists has a large effect on what conformations it will adopt. For example, placing a protein in a nonaqueous environment often destroys the biological function of the protein because drastic changes occur in the conformation of the protein. Changing the nature of the aqueous environment can cause this effect as well. For example, a substantial change in the pH or ionic strength of a solution containing a protein can destroy biological function as effectively as placing the protein in a non-aqueous environment. Less severe changes often occur naturally in the aqueous environment found in living cells. Such changes are often responsible for

29. Hydrophilicity and hydrophobicity are very important factors used by protein engineers to predict protein conformations, often through use of a concept of a "localized environment" for a protein region. This term is often used to describe the nature of a particular region of the protein under study. For example, if a region of the protein has a high concentration of hydrophilic amino acid residues, the protein engineer will normally consider the localized environment of that region to be hydrophilic. This information is useful to the protein engineer because, instead of having to actually calculate the effect of the interactions of each amino acid residue in that region, the engineer can make a rough estimate that this hydrophilic region will be on the exterior of the protein, where the protein interacts with its aqueous environment. Likewise, a stretch of amino acid residues which are predominantly hydrophobic will be expected to adopt a conformation which shields these residues from the protein's aqueous environment. Hydrophobic regions of the protein therefore are likely to be found in the interior region of the protein.

changes in levels of biological function or activity, and typically occur in response to a cellular stimulus.³⁰

The interactions between different regions of proteins discussed above have all been in the context of non-covalent interactions. Keep in mind, however, that different regions of a single polypeptide, as well as distinct polypeptides, can associate through covalent bonds as well. The most common association is the disulfide bond which forms between the side chains of two cysteine amino acids. A covalent association can greatly restrict the range of possible protein conformations for either a single polypeptide or a complex of multiple polypeptide chains, as it is a much stronger interaction than a non-covalent interaction.

There are also non-covalent, non-polypeptide, and non-environmental interactions which influence protein activity. The biological activity of many proteins often depends upon whether the protein has complexed with a co-factor, such as a metal ion. The most well-known example of such a protein is hemoglobin. If the iron co-factor of hemoglobin is removed, the ability of the protein to carry out its oxygen-transporting "biological function" is greatly diminished. This derives from the inability of the protein to adopt or retain certain conformations necessary to bind or release oxygen. Other ways of influencing the protein activity derive from post-translational modifications of the polypeptide backbone of the protein.³¹ Here, certain amino acid residues in the protein are altered either directly or by covalent attachment of other compounds, such as sugar residues.³² Often, these modifications contribute to the stability of a particular biologically active conformation.

30. For example, a cell may change its internal environment in response to a hormone binding to a cellular receptor. This change in environment can then induce a protein to adopt a particular conformation which renders the protein either active or inactive.

31. The term "post-translational modification" includes all processing done by the cell after a cell assembles the protein from free amino acids and the information stored in the DNA which codes for the particular amino acid sequence. After it has "translated" the genetic information into a polypeptide sequence, the cell will often chemically modify the translated polypeptide product to yield the mature, fully functional form of the protein. Examples of amino acid residues which result from such modifications include hydroxyproline (from proline), and gamma-carboxyglutamic acid (from glutamic acid residues). Other types of post-translational modifications do not change the structure of the amino acid side chain group, but simply attach additional functional groups to the side chains, such as sugar residues or lipids.

32. Strings of sugar residues attached to a particular amino acid side chain are termed "glycosylation." Glycosylation can affect biological activity without directly influencing protein conformation. For example, glycosylation in erythropoietin serves to enhance retention of the protein in mammals, without significantly affecting the biological activity of the protein. Without the glycosylation, erythropoietin is cleared rapidly from the bloodstream. Yet the unglycosylated protein shows nearly full biological activity when measured in *in vitro* biological assays.

A final factor bears mention. Changes made to one region of a protein will often affect other regions which then alter the tertiary structure of the protein. This introduces another level of complexity in the overall picture of interchain and environmental factors that can influence a protein's conformation. Predictions based upon a certain factor may require that other factors be held "constant." This can significantly diminish the accuracy of a protein model to the "real world" protein.

In short, a protein is subjected to a bewildering array of different factors—interdependent to some degree—which have the capability to alter and change its conformation. Yet it is the overall structure of the protein, or a specific region of the protein that is essential to the native biological activity of the protein.³³ For example, one region of a protein might play a role in associating the protein to a particular type of cellular receptor, while another region might act as a receptor for a different protein, or act to catalyze a particular reaction.³⁴ Correlating the activity of a protein with the structure of a region of the protein is one of the most difficult questions facing the protein engineer. Elucidation of this relationship between amino acid sequence, conformation, and function thus becomes the essential prerequisite for *predictive* use of amino acid sequence data. This relationship, which has been termed the "second genetic code,"³⁵ remains an elusive target.

C. What Is "Protein Engineering"?

The complexity of factors which affect protein conformation and biological activity illustrates why "engineering" a new or even modified form of a protein seems like an incomprehensibly complex task. Luckily, this is not the case. Even a cursory look at the accomplishments in the past decade in the realm of "protein engineering" shows that goals set in this area are not only possible, but attainable. Furthermore, with the

33. It is not uncommon for a single amino acid change to significantly affect the structure and activity of a particular protein. In the context of measuring the impact of substitutions of amino acid residues in conserved regions of enzymes, workers have reported decreases in the rate of catalysis ranging from a factor of 2 to a factor of more than 25,000. Leatherbarrow & Fersht, *Protein Engineering*, 1 PROTEIN ENGINEERING 7, 9 (1986). See also Cordonnier, Montagnier & Emerman, *Single Amino-Acid Changes in HIV Envelope Protein Affect Viral Tropism and Receptor Binding*, 340 NATURE 571 (1989) (changing of single residue in the envelope protein of HIV affects receptor binding capacity).

34. A good example of a well-characterized protein which has several distinct domains is t-PA. This protein has one region which catalyzes the degradation of polymeric fibrin, otherwise known as blood clots. A different region plays a role in binding to the fibrin clot.

35. "The ultimate solution to the 'protein folding problem' will be the elucidation of the 'second genetic code' relating the amino acid sequence of a protein to its secondary, tertiary, and quaternary structures." Creighton, *Protein Structures* (Book Review), 247 SCIENCE 1351 (1990).

improvements in available computing power, and the almost constant increase in the understanding of protein conformational dynamics, protein engineers are now able to predict confidently the effects of often significant structural modifications to proteins.

"Protein engineering" is a term which can have several meanings, depending upon who is asked. Generally speaking, protein engineering encompasses a range of activities whose goal is the creation of novel, non-naturally occurring protein structures. This may be accomplished by altering existing polypeptide sequences, combining segments or regions of different proteins, or by designing polypeptide sequences *de novo*. A 1986 commentary is still useful in providing additional structure to this field of technology by defining four classes of "protein engineering."³⁶ The first class of engineering work is based upon relationships which can be deduced from primary sequence information and then applied to different systems. Examples include short peptide sequences having functional significance irrespective of the regions flanking the sequence, and changes which can be made in particular residues of a peptide which are based upon knowledge of the chemical nature of the residue side chain.³⁷ The second class identified includes experiments which correlate the results of random mutations with empirical observations, but do not require specific knowledge of "fundamental structure-function relationships." The type of work falling into this class includes screening and selection procedures based on random mutations of a known sequence. The third class encompasses work done to elucidate and quantify fundamental relationships between structure and function, typically in the context of measurement of changes resulting from specific changes in sequences, and studies of homologous protein sequences from different species.³⁸ This class of work is currently viewed as being the most common form of "protein engineering." Finally, a fourth class, considered to be "true" protein engineering includes "those experiments in which a protein of improved features is confidently synthesized from a design based on well-understood structure-function relationships."³⁹

36. Wetzel, *What Is Protein Engineering?*, 1 PROTEIN ENGINEERING 3, 3-4 (1986).

37. The specific example cited was changing a residue susceptible to oxidation, such as methionine or cysteine, to an oxidatively resistant analog. This gives the modified protein an improved "shelf life" when compared to the native protein simply by removing the portion of the protein which makes the native protein susceptible to degradation.

38. A common example of this class is where a single residue is varied to assess the "tolerance" to change of that site in the primary structure. Typically this will involve production of a range of mutants varying only at the preselected residue. The activity of these species will then be measured as one means for assessing the tolerance of the site to change. This is a common procedure for enzymes, which typically interact with substrates through specific residues.

39. The number of examples of "true" protein engineering continues to grow. Highly publicized members of this group include the single chain and "chimeric" antibodies, and the Genetics Institute t-PA construct.

While certain instances of success in this last category are known, it is safe to say that this stage of protein engineering is not commonplace.⁴⁰

Advances in recombinant DNA technology during the 1980's facilitated the dramatic increase in our understanding of how proteins adopt and assume conformations. This tool allowed protein engineers to make specific changes in the primary sequence of a protein to test hypothetical models in "real world" terms in a very short time frame. This, in turn, enabled protein engineers to assess the impact of changes made to the primary sequence of a protein and then use this knowledge to make further predictions. Through this iterative process of modification and measurement, protein engineers gained the ability to deduce some preliminary, albeit generalized, conclusions regarding structure-function relationships between primary sequence data and conformational dynamics. Analyzing this empirical data led to some fairly well accepted theories as to the interchangeability of certain chemically similar amino acids, and more importantly, defined relationships which could be used to predict the general nature of conformations for wholly *de novo* polypeptide structures.⁴¹

The advances in understanding through this period have also led to certain basic conclusions. One very important conclusion, for purposes of assessing both factual and legal equivalence among modified but closely related forms of a protein, is that minor, conservative changes in protein

40. Recent work in the area of "single chain antibodies" arguably falls into this "fourth class." These entities are designed using a complex computer-based modeling program which takes two fragments of existing antibody chains, and then "engineers" a linking region to join the two fragments in a way which retains the conformations of the native antibody binding region so as to retain the original antigen-binding function.

41. The following summary illustrates the "state of the art" of the effects of genetic mutations on protein structure and conformation:

Despite the difficulty of partitioning mutational effects between the folded and unfolded states, several general conclusions are emerging:

1. The role of each amino acid depends on its structural context. Sensitivity to severe destabilizing substitutions is correlated with features of the folded state, implying that interactions in this state are often dominant. With the exception of charged residues, most amino acids that make critical interactions are rigid or buried in the folded structure.

2. Many different types of interactions—including disulfide bonds, hydrophobic forces, hydrogen bonds, electrostatic interactions, and dispersion forces—make quantitatively comparable contributions to stability.

3. Specific interactions of each type make a wide range of stabilizing contributions. The observed range of contributions is not adequately described by the behavior of the simple chemical model systems traditionally used to evaluate the strengths of noncovalent interactions. Model systems generally do not account for the unique environments of each residue in the folded and unfolded states or for the entropy changes associated with forming specific interactions.

4. Many amino acid substitutions do not have large effects on stability. Proteins tolerate substitutions because (a) some substitutions preserve critical interactions, (b) some interactions apparently do not make large contributions to stability, and (c) protein structures adjust to compensate for changes in sequence. The impact of an amino acid substitution is a combination of its intrinsic effects on the folded and unfolded states and the relative abilities of the two states to relax in response to the change. Relaxations minimize destabilizing effects.

Alber, *Mutational Effects on Protein Stability*, 58 ANN. REV. BIOCHEM. 765, 766 (1989).

sequences effected through either random mutations or site directed mutagenesis no longer can be treated as an inherently unpredictable feat. The thrust of several recent articles tends to minimize the impact of such conservative changes, concluding that a large number of conservative amino acid changes can be made without significant effects on the overall conformation and activity of the protein, as compared to the naturally occurring or wild type protein.⁴² As advances in recombinant technology, molecular modeling, and protein chemistry continue, the unraveling of the second genetic code may someday be possible. Until then, anyone venturing into the world of predictive protein engineering must recognize not only the inherent unpredictability associated with such efforts, but also that such unpredictability does not necessarily represent an insurmountable barrier to a "protein engineer" even at this early stage in the industry.

III. THE DOCTRINE OF EQUIVALENTS

The 1980's were a period of extensive scientific development for biotechnology in which a substantial advance in patent-rights interpretation took place. Leading this advance was the Court of Appeals for the Federal Circuit.⁴³ In a number of published opinions, this court addressed the question of the equitable nature of patent rights arising from expansion of these rights under the doctrine of equivalents. A brief summary of the current state of the doctrine may serve to place the question of expansion of the enforceable protection of protein patent rights clearly in focus.

A. A Current Overview of the Requirements for Use of the Doctrine of Equivalents

The doctrine of equivalents is a mechanism for a patentee to establish infringement of the patent rights. However, the doctrine is not the first issue a patentee faces in an action to prove infringement of patent rights. Only where there is no literal infringement of one or more of the patent claims does the question of through equivalents arise.⁴⁴ The issue of equivalence is a question of fact reviewed under the clearly erroneous

42. See, e.g., Bowie, Reidhaar-Olson, Lim & Sauer, *Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions*, 247 SCIENCE 1306 (1990).

43. See Kastriner, *The Revival of Confidence in the Patent System*, 73 J. PAT. OFF. SOC'Y 5, 8 (1991) (CAFC has brought about uniformity and certainty in interpretation of the patent laws, and has significantly enhanced the economic power of patents). For an extensive study of the impact of the Federal Circuit on modern patent litigation, see Dreyfuss, *The Federal Circuit: A Case Study in Specialized Courts*, 64 N.Y.U. L. REV. 1 (1989).

44. The doctrine of equivalents comes into play only when actual literal infringement is not present. *Hughes Aircraft Co. v. United States*, 717 F.2d 1351 (Fed. Cir. 1983).

standard.⁴⁵ The patentee, in this context, must show that the allegedly infringing product "performs substantially the same overall function or work, in substantially the same way, to obtain substantially the same overall result as the claimed invention."⁴⁶ Satisfaction of each of the three prongs of this test for equivalence is a condition precedent to any further analysis under the doctrine of equivalence. Meeting this burden in the context of protein claims is itself a complex process which will not be addressed in this paper.⁴⁷

Once the factual burden of proving equivalence has been met by the patentee, two questions of law can intervene to preclude extension of the patentee's patent rights.⁴⁸ Both involve the prior art in existence at the time of the patent grant.

First, the doctrine will not extend to an infringing device within the public domain, i.e., found in the prior art at the time the patent issued; second, prosecution history estoppel will not allow the patentee to recapture through equivalence certain coverage given up during prosecution.⁴⁹

Prosecution history estoppel, the second intervening question of law, is commonly raised as an affirmative defense by an alleged infringer in order to prevent a finding of infringement after equivalence has been established.⁵⁰ The success this defense depends upon the claim amendments and representations made by the patentee to the Patent

45. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 610 (1950), *reh'g denied*, 340 U.S. 845 (1950).

46. *Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931, 934 (Fed. Cir. 1987) (en banc), *cert. denied*, 485 U.S. 961, (1988), *cert. denied*, 485 U.S. 1009 (1988). The oft-quoted language adopted by the Supreme Court in *Sanitary Refrigerator v. Winters* follows:

[G]enerally speaking, one device is an infringement of another "if it performs substantially the same function in substantially the same way to obtain the same result. . . . Authorities concur that the substantial equivalent of a thing, in the sense of the patent law, is the same as the thing itself; so that if two devices do the same work in substantially the same way, and accomplish substantially the same result, they are the same, even though they differ in name, form, or shape."

280 U.S. 30, 42 (1929) (quoting *Machine Co. v. Murphy*, 97 U.S. 120, 125 (1878)).

47. Functional equivalence of proteins is a complex issue. A protein having a substantially changed structure may not function in the same manner as the native protein in terms of yielding a similar biological function. Some "functions" of the protein may be retained, while others may be lost. Does the doctrine require complete equivalence, or equivalence as to the activity of interest? These, and many other questions await a thorough analysis.

48. The application of the reverse doctrine of equivalents acting to limit a patentee's claims to a novel and nonobvious protein is a related issue which will not be addressed at this point. This doctrine awaits further development once the comments of the Federal Circuit in *Scripps Clinic* have been absorbed. See *supra* note 15. The specific question of whether the reverse doctrine of equivalents will intervene to preclude enforcement of a claim based upon isolation and purification of a naturally occurring protein against a recombinantly produced version of the protein remains to be substantively addressed.

49. *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 870 (Fed. Cir. 1985).

50. Estoppel is an affirmative defense. See Fed. R. Civ. P. 52(a).

Office during prosecution of the patent application.⁵¹ Needless to say, this is a very fact-dependent issue. However, there is an intervening question of law that has not been thoroughly considered by the courts: the degree to which the prior art may preclude a finding of equivalence.

B. The Second Burden of Proof: Patentable Hypothetical Claims

*Wilson Sporting Goods Co. v. David Geoffrey & Associates*⁵² is the first appellate decision in a half century to directly address the role of the prior art as a limit on the expansion of patent rights through the doctrine of equivalents. The Federal Circuit started its analysis in this case by reiterating the proper role of the prior art in a doctrine of equivalents analysis.

The doctrine of equivalents exists to prevent fraud on a patent, *not* to give a patentee something which he could not have lawfully obtained from the PTO had he tried. Thus, since prior art always limits what an inventor could have claimed, it limits the range of permissible equivalents of a claim.⁵³

This statement is consistent with the well-accepted view that the doctrine of equivalents "will not be used to extend a patent claim to cover a device in the public domain, i.e. found in the prior art applicable to the patent."⁵⁴ The holding in *Wilson Sporting Goods* departs from recent decisions by actually requiring the *patentee* to establish as part of his case-in-chief that the proposed scope of enforcement, cast broadly enough to

51. Prosecution history estoppel is an essential, recurring concept in the application of the doctrine equivalents. The Supreme Court has held that "[w]hatever may be the appropriate scope and application of the doctrine of equivalents, where a claim is allowed without a restrictive amendment, it has long been settled that recourse may not be had to that doctrine to recapture claims which the patentee has surrendered by amendment." *Exhibit Supply Co. v. Ace Patents Corp.*, 315 U.S. 126, 136 (1942).

The Federal Circuit also has recognized that "file wrapper estoppel" is a limit on the expansion of patent rights through the doctrine of equivalents. In *Hughes Aircraft Co. v. United States*, 717 F.2d 1351, 1363, the Court cited with approval the following text from *Autogiro Co. of Am. v. United States*, 384 F.2d 391, 400-01, (Ct. Cl. 1967):

The doctrine of equivalence [sic] is subservient to file wrapper estoppel. It may not include within its range anything that would vitiate limitations expressed before the Patent Office. Thus a patent that has been severely limited to avoid the prior art will only have a small range between it and the point beyond which it violates file wrapper estoppel.

In *Coleco Indus. v. I.T.C.*, 573 F.2d 1247, 1257 (C.C.P.A. 1978), the predecessor court to the Federal Circuit pointed out that estoppel can derive from representations made to the Patent Office as well as through actual amendments to the claims. "A patentee having argued a narrow construction for his claims before the Patent and Trademark Office (PTO) should be precluded from arguing a broader construction for the purposes of infringement." Note that prosecution history estoppel is not simply limited to estoppel created by actual amendments to the claims, but also can be based upon arguments made by the patentee to the PTO in order to obtain the patent.

52. 904 F.2d 677 (Fed. Cir. 1990), *cert. denied*, 111 S. Ct. 537 (1990).

53. *Id.* at 684 (citation omitted).

54. *Ryco v. Ag-Bag Corp.*, 857 F.2d 1418, 1426 (Fed. Cir. 1988).

cover an accused product, does not also ensnare subject matter in the public domain.⁵⁵

Before *Wilson Sporting Goods*, prior art most commonly intervened to block the expansion of patent rights through the doctrine of equivalents as prosecution history estoppel⁵⁶ raised by the alleged infringer in response to the assertion of infringement through equivalence. As such, the patentee did not have an explicit burden of proving that a finding of equivalence would ensnare the prior art as well. Thus, in one sense, *Wilson Sporting Goods* serves as a signal that the Federal Circuit intends to clarify the doctrine to reflect more accurately its equitable foundations, simply by requiring a higher standard of proof from the patentee seeking to use the doctrine to his advantage.⁵⁷

55. *Wilson Sporting Goods* is also significant in the context of clarifying what actually occurs when a patent is held to be infringed under the doctrine of equivalents. The Federal Circuit in this holding emphasized that the actual claims of the patent are not affected by an expansion of patent rights through the doctrine of equivalents.

To say that the doctrine of equivalents extends or enlarges the claims is a contradiction in terms. The claims—i.e. the scope of patent protection as defined by the claims—remains the same and application of the doctrine expands the right to exclude “equivalents” of what is claimed.

The doctrine of equivalents, by definition, involves going beyond any permissible interpretation of the claim language; i.e. it involves determining whether the accused product is “equivalent” to what is described by the claim language.

Wilson Sporting Goods, 904 F.2d at 684.

In view of this clarification, one should be careful to avoid use of the term “expanded claims” to describe the expanded scope of enforceable protection that occurs via a showing of equivalence to the claimed invention. Reference by the author to “expanded claims” in this paper is limited to those instances where this language was used in a cited decision.

56. For a substantive discussion of prosecution history estoppel, also referred to as “file wrapper estoppel,” see D. CHISUM, PATENTS § 18.02[3] (1990). As indicated therein, the leading modern Supreme Court holding on the role and application of prosecution history estoppel is *Exhibit Supply Co. v. Ace Patents Corp.*, 315 U.S. 126 (1942). *Exhibit Supply* sets forth the basic rule that narrowing of claims by a patent applicant during prosecution, if done to overcome a rejection based upon prior art, acts as a disclaimer of the subject matter so excised from the claim. If a patent applicant disagrees with the rejection, and wishes to preserve the full scope of protection sought in the claims, the proper course is appeal of the rejection.

57. The practical effect of *Wilson Sporting Goods* is that the patentee must now shoulder the burden of proving that a hypothetical claim covering the alleged equivalents would have been patentable over the prior art. 904 F.2d at 685. This is in addition to establishing the actual equivalence of the claimed invention and the accused product. 904 F.2d at 683. If the patentee fails to meet both of these burdens, then the accused infringer need not resort to any specific defenses, such as prosecution history estoppel.

While not addressed by the panel in the *Wilson Sporting Goods* decision, one would presume that the patentee would have to establish a *prima facie* case that the hypothetical claim would be novel and nonobvious over the prior art of record in the file wrapper, i.e. prior art which was considered by the patent examiner during the prosecution of the patent in question. The accused infringer, however, should be entitled to supplement the file wrapper with any additional prior art pertinent to the patentability of the hypothetical claim, and presumably the patentee would be required to disclose any prior art not contained in the file wrapper that would be equally pertinent. The patentee’s burden of establishing a *prima facie* case of patentability of the hypothetical claim and, specifically,

Placing a greater burden on the patentee also emphasizes the fact that the doctrine of equivalents is not simply an adjunct to a charge of literal infringement. Instead, it shifts the role of the prior art from primarily a defensive mechanism used to escape patent infringement to an active element necessary to establish a valid and enforceable right. The patentee must show that the prior art in existence at the time of the patent grant was insufficient to preclude a claim for the desired scope of protection. Furthermore, casting the issue as one where the patentee, rather than an accused infringer, must bear the bulk of the burden in order to stake a valid right to the accused product solidly grounds the doctrine of equivalents in an equitable framework.

1. *THE ROLE OF THE PRIOR ART AS A BARRIER TO
"BROADENED" PATENT RIGHTS BEFORE WILSON
SPORTING GOODS*

Outside the context of prosecution history estoppel, it is fair to say that prior to *Wilson Sporting Goods* there were only a handful of cases in which the issue of prior art acted as a limitation on the expansion of patent rights through the doctrine of equivalents.⁵⁸ The vast majority of references to the role of the prior art in the doctrine of equivalents analysis have been in the form of a brief, passing references in dicta to the general proposition that a patentee could not "expand his claims" to cover subject matter in the public domain.⁵⁹ This historical result may be caused by the lack of a consistent manner for interpreting prior art in the context of "broadened claims," or from the almost automatic use of prosecution history estoppel by accused infringers to thwart a patent right expansion. In any case, a summary of these past decisions helps us

novelty and nonobviousness should therefore be based on the prior art uncovered from these three sources.

58. See, e.g., *Thomas & Betts Corp. v. Litton Sys.*, 720 F.2d 1572 (Fed. Cir. 1983); *Carman v. Wahl*, 724 F.2d 932 (Fed. Cir. 1983); *Claude Neon Lights v. E. Machlett & Son*, 36 F.2d 574 (2d Cir. 1929).

59. See, e.g., *Senmed, Inc. v. Richard Allan Medical Indus.*, 888 F.2d 815, 821 (Fed. Cir. 1989) (court noted that limitations in a claim cannot be given range of equivalents so wide as to cause the claim to encompass prior art, but precluded holding infringement through equivalence under theory of prosecution history estoppel); *Tandon v. I.T.C.*, 831 F.2d 1017, 1026 (Fed. Cir. 1987) (after noting that claims may not be enlarged by equivalents to encompass the teachings of prior art, court precluded holding of infringement under doctrine of equivalents due to arguments made by patentee to procure patent from the Patent and Trademark Office); *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 870 (1985) (doctrine of equivalents will not permit extension to reach infringing device in the public domain, and a finding of infringement through the doctrine of equivalents can be blocked by prosecution history estoppel); *Perkin-Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 900 (Fed. Cir. 1984) (if equivalence is determined, infringement will be found unless prosecution history estoppel applies or if "the equivalent device is within the public domain, i.e. found in the prior art").

understand the clarification supplied by the Federal Circuit in this area through the *Wilson Sporting Goods* holding.

Prior art intervenes most effectively to block an attempted expansion of patent rights when the alleged infringer can show that the patentee actually took a position regarding the prior art during prosecution which is inconsistent with a position necessary to support expansion of the enforceable scope of the patent claims.⁶⁰ If the court is forced to delve into prior art not addressed in the prosecution, the court must consider the question of patentability of the "expanded claim" without the benefit of previous considerations of the prior art by the Patent Office or by the patentee. In addition, in the context of prosecution history estoppel, the accused infringer has traditionally borne the burden of proof in showing that the patentee did in fact forfeit the subject matter now alleged to be within the equitable enforcement rights of the issued patent claims.⁶¹ Requiring the accused infringer to raise prosecution history estoppel as an affirmative defense relieves the court of answering the sometimes difficult question of whether the "expanded claim" would have been patentable over the prior art at the time of the patent grant.

Nevertheless, a few instances exist wherein equivalence was shown, the affirmative defense of prosecution history estoppel was not raised, and prior art actually played a role in the outcome of the case. For example, the rationale from the holding in *Claude Neon Lights v. Machlett & Son*,⁶² authored by Judge Learned Hand early in this century is echoed in the opinion of the Federal Circuit in *Wilson Sporting Goods*. In *Claude Neon Lights*, the patentee attempted to expand his scope of enforceable protection to reach an electrode having an overall size which was clearly outside the literal scope of the patent claims.⁶³ Judge Hand concluded that to reach the accused electrode, the patentee's claim would have had to have been modified to remove the one element which rendered it patentable over the prior art.⁶⁴ He then pointed out that it was the patentee's burden to establish that such a construction could be made in order to define an "expanded claim" which would both reach the accused device and which would be patentable over the prior art.⁶⁵ As he stated, "even though we were to agree that [the accused electrode was an equivalent], we should still be faced with the question whether the added

60. See, e.g., *Coleco Indus. v. I.T.C.*, 573 F.2d 1247, 1258 (C.C.P.A. 1978).

61. Note that the issue of estoppel arises only after equivalence has been established: "Assuming the three-pronged test establishes equivalency between the claims and the infringing device, the extent to which the doctrine is utilized by a court to benefit the patentee is measured by estoppels arising from the prosecution history." *Id.* at 1257-58.

62. 36 F.2d 574.

63. *Id.* at 575.

64. *Id.* at 578.

65. *Id.*

matter so included involved invention. The plaintiff has the burden of proof on that issue and has not carried it."⁶⁶

Perhaps the most recent case presenting an analysis similar to the *Wilson Sporting Goods* framework is *Thomas & Betts Corp. v. Litton Systems*.⁶⁷ In this case, the patentee asserted that a single strut electrical connector produced by Litton Systems infringed its claimed double strut connector.⁶⁸ Litton had modified its original parallel double strut connector design in response to an action for infringement by T & B, and had represented to its licensee that the change would not be detrimental to the function of the connector.⁶⁹ The district court held that the difference between the claimed invention and the accused connector precluded a finding of literal infringement.⁷⁰ The court then refused to permit extension of the scope of the patent claims to cover the accused device through the doctrine of equivalents, despite having concluded that the accused device was an equivalent to the device defined by the claims.⁷¹ The court pointed out that the claimed connector, construed "sufficiently broadly" to encompass the accused connector, would have been obvious to the person of ordinary skill in view of the prior art at the time of the patent grant.⁷²

In reversing the holding of obviousness of the "expanded claim," the Federal Circuit stressed that the "subject matter as a whole" must be found to have been obvious in view of the prior art.⁷³ The subject matter as a whole was defined by the subject matter encompassed within the "broadened" claim. The Court also emphasized that even though the patented invention did not enjoy status as a "pioneer", it was still entitled to a defined, albeit narrower, range of equivalents.⁷⁴ As the court stated,

66. *Id.*

67. 720 F.2d 1572 (Fed. Cir 1983). The court emphasized that the validity of the actual claims in the patent was not to be questioned when assessing the patentability of the subject matter defined by the scope of equivalents: "[A]lthough the effect of the prior art on the scope of the claims in suit is to be considered, our approach should not be a 'camouflaged or back-handed attack' on the validity of the . . . patent." *Id.* at 1580.

68. *Id.* at 1573.

69. *Id.*

70. *Id.* at 1574.

71. *Id.*

72. *Id.*

73. *Id.* at 1581 (quoting 35 U.S.C. § 103).

74. *Id.* The stature of the invention is often relied upon by courts and others in determining the appropriate scope of equivalents to which the patentee is entitled. For example, Chisum identifies three categories for classifying ranges of equivalents; "pioneers, entitled to a broad range of equivalents; marked improvements, entitled to a substantial range of equivalents; and narrow improvements, entitled to limited or no range of equivalents." D. CHISUM, *supra* note 56, § 18.04[2] (citations omitted). This view is not new. The Supreme Court, for instance, identified the distinction between "pioneering" and lesser inventions in a number of early decisions. See *Continental Paper Bag Co. v. Eastern Paper Bag Co.*, 210 U.S. 405, 415 (1908) (not only pioneer patents are entitled to invoke doctrine, but range of equivalents depends on degree of invention);

"while a pioneer invention is entitled to a broad application of the doctrine of equivalents, an invention representing only a modest advance over the prior art is given a more restricted (narrower range) application of the doctrine."⁷⁵ The critical element, then, was defining the range of equivalents to reach the accused infringing product while remaining valid over the prior art. Considering the invention based upon the "expanded claim" as a whole, the court concluded it would not have been obvious to a person of ordinary skill in the art.⁷⁶

Similarly, *Carmen Industries v. Wahl*⁷⁷ involved a question of equivalence between two devices which promoted the flow of agricultural solids that have poor flow characteristics through the use of a vibrating device attached to the base of a hopper or storage bin.⁷⁸ The invention, as defined by the claims, required that the device have "material-receiving members" which were *concave*⁷⁹ The district court held that although the accused device, which had a *conical* material-receiving member, did not fall within the literal scope of the claims, it was nevertheless a legal equivalent of the claimed device.⁸⁰ It then conducted an exhaustive analysis and held that the "proposed construction of the claims under the doctrine of equivalents" satisfied the requirements of patentability over the prior art.⁸¹ The Federal Circuit upheld the lower court's finding that equivalence had been demonstrated, and agreed with

Cimiotti Unhairing Co. v. American Fur Refining Co., 198 U.S. 399, 407 (1905) (greater liberality permitted when invention is of a pioneer character than when it is simply an improvement); *Westinghouse v. Boyden Power Brake Co.*, 170 U.S. 537, 561-62 (1898) (claims to pioneering inventions entitled to more liberal construction).

The Federal Circuit has also recognized such a "sliding scale" of ranges of equivalents. See, e.g., *Texas Instruments*, 805 F.2d at 1563 ("It has long been recognized that the range of permissible equivalents depends upon the extent and nature of the invention, and may be more generously interpreted for a basic invention than for a less dramatic technological advance.").

In the post-*Wilson Sporting Goods* setting, however, the question of whether an invention is pioneering or incremental may serve a much reduced role. By requiring the patentee to compare the proposed "hypothetical claim" to the prior art, the court will be given an opportunity to assess exactly how significant an advance the patented invention actually was. If there is no prior art even close to the hypothetical claim, then there will be a "de facto" pioneering stature assigned to the patented invention. If, on the other hand, there is an abundance of prior art surrounding the hypothetical claim, forcing the patentee to restrict its scope so as to be closer to the actual patent claims, the invention will assume the "incremental" rather than pioneering status. What significance, if any, remains of the pioneering status label after *Wilson Sporting Goods* is yet to be determined.

75. *Thomas & Betts*, 720 F.2d at 1580.

76. *Id.* at 1582.

77. 724 F.2d 932 (Fed. Cir. 1983).

78. *Id.* at 934.

79. *Id.*

80. *Id.* at 936.

81. *Id.*

the district court that "in spite of the broadening effect of the doctrine of equivalents," the claims remained patentable over the prior art.⁸²

Finally, in *Ryco v. Ag-Bag Corp.*,⁸³ the Federal Circuit upheld a lower court's determination of infringement through equivalence of two agricultural bagging machines.⁸⁴ The court rejected the assertions of Ryco that the lower court had improperly "extended the scope" of the claimed bagger so as to encompass a prior art bagger.⁸⁵ In so holding, the court compared the *accused product* to the prior art bagger and found that the accused product functioned more like the claimed bagger than the prior art baggers.⁸⁶ The court concluded that "Ryco had substituted an equivalent of the required element of the claim thereby appropriating the benefits of the invention while technically escaping the claim language."⁸⁷ The court's framing of the issue in this case was specifically rejected in *Wilson Sporting Goods*. Nonetheless, the central issue underlying the decision clearly was, in fact, whether the prior art should preclude the "expansion of the claims" to cover the accused device.

2. THE "HYPOTHETICAL CLAIM" PRIOR ART TEST FROM WILSON SPORTING GOODS

The analysis presented in *Wilson Sporting Goods* provides a general framework in which to assess the impact of prior art upon a doctrine of equivalents patent right expansion. The Federal Circuit instructs us to "visualize a hypothetical claim" which would be broad enough in scope to *literally* read upon or cover the accused product.⁸⁸ It is this hypothetical claim that is to be compared against the prior art at the time of the patent grant.⁸⁹ If the hypothetical claim could have been allowed by the Patent Office in view of the prior art, then prior art is not a bar to the expansion of the claim to cover the accused device. If the hypothetical claim would not have been patentable over the prior art at the time of the

82. *Id.* at 942.

83. 857 F.2d 1418 (Fed. Cir. 1988).

84. *Id.* at 1420.

85. *Id.* at 1426.

86. *Id.*

87. *Id.*

88. 904 F.2d 677, 684 (Fed. Cir. 1990), *cert. denied*, 111 S. Ct. 537 (1990).

89. *Id.* Constructing hypothetical claims in relatively predictable technologies, such as golf ball design should not present a significant conceptual hurdle. Constructing hypothetical claims in areas such as protein chemistry, on the other hand, represents an excursion into complexity. For example, to reach a protein in which a competitor has changed one amino acid residue with no discernible effect, the patentee could phrase the claim as "a polypeptide sufficiently similar to sequence XYZ so as to retain biological activity W." Alternatively, the claim can be constructed to read "A protein having sequence AxBC," where x denotes a markush group of the actual amino acid residue and the residue replaced by the accused party. The discussion of hypothetical claim constructions presented *infra* pp. 130-133, addresses this issue in depth.

patent grant, then it is improper to permit the patentee to enforce that scope of protection in an infringement suit through the doctrine of equivalents. Even if the accused product is a factual "equivalent" of the claimed invention, there can be no infringement if the "hypothetical claim" would ensnare subject matter in the public domain at the time of the patent grant.

As noted earlier, *Wilson Sporting Goods* is significant because it shifts the burden of proving that the "hypothetical claim" would have been patentable *at the time of the patent grant*. As the Federal Circuit noted, "the patent owner has always borne the burden of proving infringement."⁹⁰ Essentially, this burden requires the patentee to establish that the hypothetical claim would have been found patentable by the Patent Office over the prior art *had the hypothetical claim originally been presented*. Prior art, as noted earlier, should include all prior art in existence at the time of the patent grant, whether it was cited during prosecution, or whether it is provided by the accused infringer to show that the hypothetical claim would not have been patentable.⁹¹ In predictable or established technologies, proving that a hypothetical claim would have been patentable at the time of its application should not present a significant problem for the patentee. It is in the less predictable, or even unpredictable areas, such as protein chemistry and molecular biology, that the patentability of a "hypothetical claim" will prove to be a significant burden.

3. THE "HYPOTHETICAL CLAIM" TEST APPLIED

The hypothetical claim test from *Wilson Sporting Goods* is designed to provide a consistent, understandable mechanism for courts to use in assessing whether a desired scope of enforceable protection would be permissible in view of the prior art. As the court stated, "[v]iewing the issue in this manner allows use of traditional patentability rules and permits a more precise analysis than determining whether an *accused product* (which has no claim limitations on which to focus) would have been obvious in view of the prior art."⁹² This test is applied for the sole purpose of assessing the patentability of a hypothetical claim over the prior art in existence at the time of the patent grant.⁹³ The court assessing

90. *Wilson Sporting Goods*, 904 F.2d at 685. See also *Claude Neon Lights*, 36 F.2d at 580.

91. See *supra* note 58.

92. *Wilson Sporting Goods*, 904 F.2d at 684 (emphasis in original).

93. *Id.* Despite the clear language presented in *Wilson Sporting Goods*, some commentators have questioned whether the requirements of 35 U.S.C. § 112 must be met pursuant to the proof of patentability of a proposed hypothetical claim. See, Parker, *Doctrine of Equivalents Analysis After Wilson Sporting Goods: The Hypothetical Claim Hydra*, 18 A.I.P.L.A. Q.J. 262 (1991). Delving into this question ignores the basic purpose of the test; namely to provide a consistent framework for assessing the significance of prior art against a scope of protection which the patentee does not actually have, but instead is

this argument must therefore conduct a "quasi-examination" of the hypothetical claim to assess its patentability over the prior art.⁹⁴

The first post-*Wilson* appellate decision to apply this "hypothetical claim" analysis did so in an almost cursory fashion. In *Insta-Foam Products v. Universal Foam Systems*,⁹⁵ the Federal Circuit did not require the hypothetical claim test to be satisfied by the patentee, but did use the analysis to reject the accused infringer's contention that the proposed expansion of protection should be precluded because of the prior art.⁹⁶ Then, in *Hormone Research Foundation v. Genentech*,⁹⁷ the Federal Circuit instructed the district court, on remand, to use the *Wilson Sporting Goods* framework if it found that prosecution history estoppel would not preclude a finding of equivalence.⁹⁸ Again, the court failed to explicitly require the patentee to show that the proposed expanded scope of protection would have been patentable over the prior art as part of its basic proof.

Finally, in *Key Manufacturing Group v. Microdot, Inc.*,⁹⁹ the Federal Circuit revisited and clarified the "hypothetical claim" approach of *Wilson Sporting Goods*.¹⁰⁰ First, the court pointed out that the use of the

seeking through equity. See, e.g., *Wilson Sporting Goods*, 904 F.2d at 684. Whether the party is entitled to an expansion of patent rights based upon the contribution to the advancement in technology is addressed through the question of factual equivalence in the first stage of the doctrine of equivalents analysis.

94. Judge Rich, shortly after the *Wilson Sporting Goods* opinion, discussed the role of the prior art in limiting expansion of patent rights through the doctrine of equivalents as follows:

Several recent opinions in the Federal Circuit have stated that there are two limitations on the application of the doctrine of equivalents. *First*, claims cannot be construed so broadly under the doctrine that they *would be invalid in view of the prior art*. *Second*, claims cannot be so construed as to recapture what was given up during prosecution of the application for patent in order to obtain allowance of the claim, which is known as "*file wrapper estoppel*."

The first exception or limitation is simply a special application of the general rule that a claim cannot be construed so broadly that it will read on or be obvious in view of the prior art. If that construction be given it, then it covers subject matter which is unpatentable under the statute. What it amounts to is that the court has to consider the validity of the claim in the form in which the patentee wishes to have it construed by application of the doctrine. All prior art known by the time of trial must be considered, not merely that cited by the examiner.

Rich, *Extent of Protection and Interpretation of Claims—American Perspectives*, 21 INT'L REV. INDUS. PROP. & COPYRIGHT L. 497, 507 (1990).

95. 906 F.2d 698 (Fed. Cir. 1990).

96. *Id.* at 704. The Federal Circuit, after reiterating the role of the prior art in a doctrine of equivalents analysis, held

[t]hat truism, however, is of no avail to Universal because, in the terminology of *Wilson*, the hypothetical claim drawn to encompass Universal's gun would not have been unpatentable under 35 U.S.C. § 103 in view of the Johnson patent. The latter would not have motivated one of ordinary skill in the art to employ an external rather than internal biasing means.

Id. This somewhat cursory assessment of obviousness of the hypothetical claim was made without explanation beyond what is cited here.

97. 904 F.2d 1558 (Fed. Cir. 1990).

98. *Id.* at 1569

99. 925 F.2d 1444 (Fed. Cir. 1991).

100. *Id.* at 1449.

hypothetical claim analysis was not a mandatory procedure, but was instead a way to "help define the limits imposed by prior art on the range of equivalents."¹⁰¹ The second point made by the court was that the patentability assessment was not intended to rise to the level of a "full blown patentability analysis."¹⁰² Instead, the court seemed to imply that the hypothetical claim framework was more like a screening procedure to measure a proposed scope of enforceability against the prior art in existence at the time of the patent grant. The court then applied such a screening test and found that a hypothetical claim sufficiently broad to reach the Microdot's product would have been obvious over the prior art.¹⁰³ Accordingly, the court reversed the lower court's finding of infringement through equivalents.¹⁰⁴

The process of clarifying of the "hypothetical claim" test for prior art continued in the holding of *Jurgens v. McKasy*.¹⁰⁵ In that case, the plaintiffs had sued for and obtained a finding of infringement through equivalence of a wind sock duck decoy.¹⁰⁶ The findings of the jury were not challenged at trial by the defendants. This allowed the Federal Circuit to review the question of infringement through equivalents essentially as a question of law.¹⁰⁷ First, the panel classified the "hypothetical claim" question as being one of law with factual underpinnings, citing the holdings of *Loctite* and *Wilson Sporting Goods*.¹⁰⁸ The panel then constructed a "hypothetical patent claim—similar to the asserted claim but broad enough to literally cover the accused products" and tested "whether that claim would have been patentable in view of the prior art."¹⁰⁹ The court found that such a claim was identical to the existing patent claims, except for the removal of limitations on the arrangement of the elements of the windsock which had originally placed the accused product outside of the literal scope of the claims.¹¹⁰ The court then turned to a conclusion of the jury that a certain element in the prior art which showed this arrangement of elements was not relevant to the patented windsock because the cited disclosure was not analogous art. This finding, the court held, justified its conclusion that the "hypothetical claim" in question would not have been rendered unpatentable by the

101. *Id.*

102. *Id.*

103. *Id.*

104. *Id.*

105. 927 F.2d 1552 (Fed. Cir. 1991).

106. *Id.* at 1555.

107. The failure of the defendants to challenge the jury's finding of factual equivalence led to a summary disposal of this aspect of the defendant's appeal on review, leaving only the legal question of equivalence for the court. *Id.* at 1561.

108. *Id.*

109. *Id.*

110. *Id.*

prior art.¹¹¹ Therefore, the court affirmed the legal conclusion of infringement through equivalence.¹¹²

The posture of the Federal Circuit in these post-*Wilson Sporting Goods* decisions tends to downplay the prospect of the hypothetical claim test becoming an unmanageable and threatening burden for patentees. While the court does classify the question of patentability of the hypothetical claim over the prior art as one of law, it appears that the court will look to the conclusions of the fact finder to assess the significance of the prior art. The hypothetical claim test should not force courts to take the place of the Patent and Trademark Office, conducting *de novo* examinations of proposed claims and assessing their patentability in view of all the statutory patent guidelines. Nor is it likely that the test will require extensive excursions into prior art, assessing in detail the significance of individual disclosures. As Judge Rich pointed out, this test is merely a means for assessing the significance of the prior art using an analysis with which the courts are familiar: the questions of novelty and nonobviousness.¹¹³

IV. APPLYING THE HYPOTHETICAL CLAIM TEST TO PROTEIN PATENTS

The progress of the prior art at the time the patent application was filed is critical to a hypothetical claim analysis. First, since the effect of the prior art upon expanded patent rights is to be measured at the time of

111. *Id.* at 1561–62.

112. *Id.* at 1562.

113. *See supra* note 95. A fear that this hypothetical claim framework lessens the presumption of validity that is attached to issued patents seems unfounded as well. Parker, *supra* note 94, at 276. The text of *Wilson Sporting Goods* provides several reminders that any assessment under the doctrine of equivalents necessarily involves going outside of the patentee's actual claims. The merits of a hypothetical claim outside the context of measuring and assessing the prior art are irrelevant, simply because they are not actual claims. As the court emphasizes, "[t]he doctrine of equivalents, by definition, involves going beyond any permissible interpretation of claim language." *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684 (Fed. Cir. 1990), *cert. denied*, 111 S. Ct. 537 (1990). Conclusions reached concerning the patentability of a hypothetical claim over the prior art have no effect and no bearing on the question of validity of the actual claims. "Wilson's claims remain valid whether or not Wilson persuades us that it is entitled to the range of equivalents sought here." *Id.* at 685.

Many practical questions regarding implementation of the hypothetical claim test, however, remain to be elucidated. For example, although the patentee is to shoulder the burden of proving that the proposed scope of protection would have been patentable over the prior art, it is unclear what sort of burden will be imposed on the patentee to search and provide prior art beyond what was considered in the original prosecution. Even more perplexing is any expectation of the court that a patentee will adopt a detailed theory as to such a claim's patentability which differs in any form from that already present in the prosecution history for the original claims. Thus, patentees may approach this burden of proof by adopting a simple *pro forma* statement of patentability based upon the rationale used in the prosecution history.

the patent grant, the patentee must ascertain what the prior art would have meant to the person of ordinary skill at that time.¹¹⁴ Second, whether a novel species of protein encompassed by a hypothetical claim would have been obvious to the ordinary worker rather than "obvious to try"¹¹⁵ will depend upon factors such as whether the primary structure was known, or whether any structure-function relationships had been elucidated. The successful application of this "hypothetical claim" approach requires the patentee to first identify the prior art in existence at the time the patent application was filed; second, to ascertain the level of skill of the ordinary worker at that time; and finally, to demonstrate that the prior art would neither have anticipated, nor would have made obvious, the protein species defined by the hypothetical claim.

A. A Typical Evolution of Prior Art Following Protein Discovery

A very general summary of a typical progression that is observed once a novel protein or activity has been identified may be set out as follows.

1. Stage One: the protein is isolated and purified from natural sources;
 - a) Unique biological activity is discovered in purified extract and assigned to an identifiable protein species;

114. "[T]he doctrine will not extend to an an infringing device within the public domain, i.e., found in the prior art *at the time the patent issued.*" *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 870 (Fed. Cir. 1985) (emphasis added). This statement, taken literally, is at odds with the requirement that patentability be assessed at the time the patent was applied for, rather than at the time of its examination and issuance. In proving patentability of the hypothetical claim, it must follow that one must assess the state of the art, and ascertain the level of skill at the time the patent application was filed. The notorious backlog in biotechnology related patent applications at the Patent & Trademark Office has created a situation where one cannot realistically equate the level of skill at the time of application with that at the time of issuance of the patent (e.g. an application filed in 1984 may not have issued until 1990). Where technology is rapidly maturing, as in protein chemistry, such 3 to 5 year delays can have a significant impact on interpretations of the "ordinary level of skill in the art." As the Federal Circuit stated, it is essential that the decisionmaker forget what he or she has been taught at trial about the claimed invention and cast the mind back to the time the invention was made . . . to occupy the mind of one skilled in the art who is presented only with the references, and who is normally guided by the then-accepted wisdom in the art.

W.L. Gore & Assocs., v. Garlock, Inc., 721 F.2d 1540, 1553 (Fed.Cir. 1983), *cert. denied*, 469 U.S. 851 (1984).

It should be kept in mind that the accused infringer has a potentially critical role in ensuring that all relevant prior art is before the court before it attempts to assess the patentability of a hypothetical claim. Since the hypothetical claim analysis involves the comparison of subject matter beyond what was considered by the patent examiner during prosecution, there is a grave potential for prior art not in the file wrapper to play a significant role in determining the patentability of the hypothetical claim. *See supra* note 58.

115. For a discussion of the "obvious to try" doctrine, see *infra* note 132.

- b) Protein is purified using conventional techniques to an essentially homogeneous level;
 - c) Primary structure is partially identified (e.g. N-terminal amino acid sequence elucidated), presence of post-translational modifications are detected.
2. Stage Two: the primary structure of the protein is elucidated and the protein is expressed by recombinant techniques;
 - a) Gene coding for the protein is ascertained through the use of DNA probes; full sequence for the protein is predicted;
 - b) Protein is expressed recombinantly so it possesses biological function, full sequence of protein is verified.
 3. Stage Three: novel protein sequences are designed and expressed;
 - a) Site-directed mutagenesis is used to identify amino acid residues essential to proper structure and function of the protein, elucidation of secondary sequence;
 - b) Molecular modeling, x-ray crystallography, and genetic mutational studies used to elucidate sequence-structure-function relationships;
 - c) Non-naturally occurring species of peptides and proteins designed and expressed based upon knowledge of sequence-structure-function relationships of the isolated protein.¹¹⁶

The purpose behind outlining this generalized progression in the art is to focus the reader's attention on a situation which is somewhat unusual when considering the impact of prior art upon a particular claimed protein. Until *de novo* protein engineering is possible, the protein engineer must first identify and isolate a protein from natural sources before expressing a wild type protein in recombinant form and producing non-naturally occurring forms of a protein. In other words, a person of

116. A final stage which is not realistically included in this paper is *de novo* protein synthesis not based upon known sequences. Four years ago, the following summary represented a fair estimate of the state of the art: Designing proteins *de novo* is the Holy Grail of the protein engineer. The greatest challenge of all is to create a functional enzyme or protein—properly folded—from first principles. And the obstacles are staggering. To date, it is still not possible to predict the tertiary structure of a protein from its amino acid sequence—unless that sequence is very homologous to some other protein whose X-ray crystallographic structure is already known. Van Brunt, *Protein Architecture: Designing from the Ground up*, 4 *BIO/TECHNOLOGY* 277 (1986).

At this time, *de novo* protein design and synthesis remains at a rudimentary stage, concentrating more on the successful prediction of protein conformations rather than on an attempt to predict biological function associated with different conceptual conformations. Advances in computing power, increased amounts of structural data, and instances of success all have led to incremental advances, yet by no means can one say that the "Holy Grail" is within reach. See also DeGrado, Wasserman & Lear, *Protein Design, a Minimalist Approach*, 243 *SCIENCE* 622-28 (1989) (hereinafter DeGrado).

ordinary skill in the protein engineering art cannot at this time adapt existing knowledge of protein structure and function to produce a completely new protein entity. The overall "machinery" of discovery, isolation, purification, and characterization available to the skilled worker are of little help in "inventing" a previously unknown protein. Until the naturally occurring species is discovered and characterized at least to a partial degree, the later stages of invention are simply not possible.

Again, this summary is not intended to cover every possible situation; instead it presents a general progression that usually follows the discovery of a new protein. Likewise, an attempt to identify and address every possible interaction between the prior art and a hypothetical protein claim would be both futile and incomplete. Rather than attempt to categorize and predict the outcomes of all such potential interactions, this paper focuses on a few key points that need to be considered when construing the effect prior art has on hypothetical "expanded" claims.

B. A Purified Protein Patent Has a "Quasi-Pioneering" Stature

A patentee holding a claim based upon isolation and purification of a protein from "natural" sources is not likely to encounter problems from the prior art when seeking to expand patent rights through the doctrine of equivalents. Generally speaking, the discovery of a new protein has a "pioneering stature" because, unlike new compounds produced through chemical synthesis, a newly discovered protein having a novel activity or "function" could not have been "predicted" or even contemplated prior to its actual discovery. At most, the prior art at the time of the patent grant will have disclosed the protein in an unpurified, or less purified state.¹¹⁷ Also, this sort of absence of "significant" prior art is often viewed by the courts as an important factor when assessing whether or not an invention should be classified as "pioneering."¹¹⁸ Yet, the successful identification and isolation of a new species of protein does not typically rise to the level of a truly pioneering invention when measured in terms of the conventional procedures used to identify, isolate, produce and purify, proteins.¹¹⁹ In this respect, the "pioneering" aspect of a new

117. The presumption underlying this conclusion is that an increased purity led to the finding of patentability of the protein claim. If the prior art teaches a protein having the same level of purity and activity, it should not be possible to obtain a claim to a protein lacking some qualifying parameters drawn to purity or activity. Typically, when a protein is expressed by a recombinant host, routine procedures permit recovery of high purity protein.

118. For example, in *Texas Instruments v. I.T.C.*, the Federal Circuit found persuasive the absence of "significant" prior art in holding the electronic hand-held calculator of T.I. to be a "pioneering" invention. 805 F.2d 1558, 1572 (Fed. Cir. 1986).

119. The Federal Circuit in *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991), provided a good example for this "quasi-pioneering" characterization.

protein discovery stems from the inherent unpredictability of the discovery itself.

Prior art insufficient to have made "obvious" or to have "anticipated" the *actually* claimed protein at the time of the patent grant is also not likely to be construed to render a hypothetical claim to a protein unpatentable, at least where the levels of purity are equal.¹²⁰ As the court reminds us in *Wilson Sporting Goods*, the pertinent question is "whether that hypothetical claim could have been allowed by the PTO over the prior art."¹²¹ The patentee in this situation must show that a hypothetical claim can be written which encompasses the accused protein without ensnaring *less purified*, naturally derived protein compositions. This burden is not expected to be formidable. Accordingly, a newly discovered and isolated protein species can have a pioneering nature at least with respect to the limiting impact of the prior art.

C. Hypothetical Claims Based Upon Patented Native Sequence Recombinant Proteins

A patentee holding a claim to a native sequence protein produced through recombinant procedures is in a situation analogous to the patentee with a claim based upon purified protein work. In such a scenario, it is likely that the protein engineer had to solve some problems prior to successfully expressing a fully functional native sequence protein by recombinant means. It is the resolution of these problems, not the superiority of the recombinant product over existing prior art, that will persuade the examiner to allow the claim. As such, the prior art the patent applicant must distinguish is not "significant" in the sense that it was not sufficient to bar the allowance of a claim to a protein having the same sequence expressed through recombinant means. This same prior art will not be capable of precluding expansion of patent rights to subsequent efforts (e.g. non-native sequence proteins). Since patentability will often be based on the expression of the recombinant gene rather than the protein itself, the prior art should not bar hypothetical claims to

There the court found that Amgen had achieved a simultaneous conception and reduction to practice through the successful characterization and subsequent expression of the erythropoietin protein. *Id.* at 1205. It noted that even though the procedures used by Amgen had been commonly used and known prior to their application to the erythropoietin problem, there was a level of uncertainty and unpredictability associated with the successful application of these techniques to yield erythropoietin. *Id.* at 1208-09.

120. Whether the target of the "expanded claims" is a recombinant version of the protein having a primary structure identical to or distinct from that of the native protein is irrelevant as these species represent later stages of invention that would not have been possible absent the actual discovery and characterization of the new protein. In assessing such hypothetically claimed proteins, keep in mind that the recombinant version will have a purity and activity typically at least as high as the protein teachings which served as the basis for the patent.

121. *Wilson Sporting Goods*, 904 F.2d at 684.

recombinant expression of non-native sequence proteins.¹²² Any other result would raise questions as to the validity of the patented protein claim itself.

D. Limitations of the Prior Art Arise for "Mutant" Proteins

The first stage at which the prior art will realistically act to limit expansion of patent rights occurs where the patentee holds a claim to a non-naturally occurring species derived from a known protein.¹²³ Here, the patentee's claimed species is likely to have a different primary structure than the species of protein found in nature, or will differ through the absence or modification of the post-translational chemical modifications possessed by the naturally occurring species. In both situations, the patentee is likely to have obtained protection for a species of protein because of a material distinction in the protein as compared to the way the protein is found in nature, or as it is produced through conventional recombinant techniques. The material distinction is assumed to have provided the basis for the finding that the mutant protein species itself was patentable over the prior art. For simplicity, this analysis will focus on the scenario in which only the primary structure of the protein has been altered.

1. PRACTICAL PROBLEMS IN CONSTRUCTION AND PROOF OF PATENTABILITY OF HYPOTHETICAL MUTANT PROTEIN CLAIMS

The patentee faces the practical problem of *constructing* a hypothetical claim which reads upon both the patented protein and the accused protein, but which does not ensnare the naturally occurring species of the protein. How this claim is constructed will directly influence the outcome of the "hypothetical claim" approach. If the hypothetical claim is patentable over the prior art, the prior art will not limit the expansion of patent rights sought by the patentee.

How the patentee will actually structure the hypothetical claim is highly dependent upon the relationship between the patented and accused species of proteins. Two important factors to consider when assessing both the patented species and the accused species include the extent of change of the primary structure (e.g., single residue changed, removal of portion of the sequence, addition of non-native sequence) and

122. The target of the expansion of patent rights will normally represent a stage of invention at or beyond that which the patented protein represents.

123. For the sake of simplicity, a protein which has been modified so as to be different from the protein as it is found in nature will be called a "mutant." Also, a basic assumption that the prior art discloses the full length primary structure of the protein has been made for the purposes of this discussion.

the introduction of any novel functions into the mutated species (e.g., diminished or enhanced biological function or activity as compared to native species, additional activities not possessed by native species). In this context, the hypothetical claim will have to vary in its use of structural and functional terms so as to ensure that the proposed "literal scope" reaches both the patented and the accused species. Where the accused species has a substantially altered primary sequence relative to the patented sequence, as well as to the native sequence, a function-oriented hypothetical claim may be necessary to reach it. However, because the use of function-oriented terms in a claim tends to increase the number of prior art species falling within its "literal" scope, the hypothetical claim is less likely to be patentable.

(a) *A "Hypothetical Markush Group" Claim*

A hypothetical claim theoretically could be cast as a simple markush group consisting of the accused mutant and the claimed mutant. Here, the focus of the "hypothetical" claimed mutant is, of course, *directly* on the accused species. It follows then, that if the accused species differs significantly from the native sequence, or changes the activity or stability of the protein, it will likely be found patentable over the art at the time of the patent grant. This is because the first species of the markush type claim has already been held to have been patentable.¹²⁴ In essence, the burden facing the patentee in this approach will be to establish that the accused mutant protein would have been patentable over the art at the time of the patent grant.

The markush-type approach is problematic because it falls back on the type of comparison that the Federal Circuit specifically instructs us *not* to adopt in construing the effect of the prior art. The court in *Wilson Sporting Goods* was critical of earlier judicial opinions which compared the accused product to the prior art in assessing whether the prior art would serve to prevent expansion of patent rights through a finding of equivalence. Such a comparison negates the benefit envisioned through the hypothetical claim approach. "Viewing the issue [as a hypothetical broadened claim] allows use of traditional patentability rules and permits a more precise analysis than determining whether an accused product (which has no claim limitations on which to focus) would have been obvious in view of the prior art."¹²⁵ There is an obvious risk then that a simple markush group will be held to improperly focus on the accused species of protein.

124. The court indicated in *Wilson Sporting Goods* that the validity of the actual claims was not at issue when considering the patentability of the hypothetical claim during a doctrine of equivalents analysis. 904 F.2d at 684.

125. *Id.*

(b) *Broad "Function-Oriented" Hypothetical Claims*

At the other extreme is the hypothetical claim cast in predominantly functional terms. Use of functional terms without structural limits presents two problems. First, the patentee may not be able to even *identify* the range of species falling within a predominantly functional hypothetical claim. For example, if a claim simply reads "a protein having function Z of protein X where at least one residue has been changed, deleted, or added in the native sequence of protein X," ascertaining which species actually do retain the function Z will prove to be a practically impossible task.¹²⁶ Second, the absence of enough qualifying structural elements will result in a claim that literally encompasses an enormous number of species of new sequences. The risk in this scenario is that one or more species falling within the literal scope of the hypothetical claim will be found to have been unpatentable over the prior art, thereby negating the proposed expansion of patent rights.

At this point in time, there is insufficient guidance from the courts to ascertain which of the various approaches is proper. From the perspective of the patentee seeking to establish that a hypothetical claim would have been patentable, obviously the markush group approach simplifies the task. In any case, an understanding of the issues of patentability facing the patentee is essential.

2. PATENTABILITY ISSUES

Once the hypothetical claim has been defined by the patentee, it must be shown to have been patentable over the prior art at the time of the patent grant. In practice this burden will boil down to the question of whether the mutated protein would have been obvious in view of the prior art. This conclusion stems from the simple recognition that if the hypothetical claim is drawn to reach species actually disclosed in prior art prior to the filing of the patentee's application, the hypothetical claim would have been unpatentable due to anticipation. Also note that in this type of scenario, where the patentee holds a patent to a mutant species, it is very likely that the native sequence species was fully disclosed at the time of the patent grant.

Assessing obviousness of a novel protein sequence is not a simple exercise, and is highly fact dependent. Some common issues, however,

126. This problem is illustrated well by the Federal Circuit's affirmation of the finding of invalidity due to a lack of enablement in *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991). The district court found that over 3,600 different EPO analogs can be made by substituting at only a single amino acid position, and over a million different analogs can be made by substituting three amino acids. After five years of experimentation, the court noted, "Amgen is still unable to specify which analogs have the biological properties set forth in claim 7." *Id.* at 1213.

can be identified.¹²⁷ First, if the change introduced affects the activity or function of the protein in a positive or desirable manner, an argument focusing on the inability to accurately predict such a change should be persuasive in establishing nonobviousness of the change. Likewise, if the primary structure of the native protein is significantly altered (e.g., large domains or regions removed), unpredictability of the effects of that change should fall into the same category of nonobvious modifications. If, on the other hand, the change is a "conservative" change, or if the change is one which has been routinely successful in analogous protein systems, the burden of establishing that such a species was nonobvious may be difficult to meet, especially in view of the recent revival of structural obviousness.¹²⁸ The burden facing the patentee requires recognition of which of the two situations is present, and how to best cast the claim in the context of the former, rather than the latter.

(a) *Conservatively Changed Mutants as Structurally Obvious Homologs or Analogs*

By the mid-1980's, advances in DNA techniques, particularly site directed-mutagenesis, enabled the average worker in this field to confidently produce a wide range of closely homologous species of proteins based upon a fully characterized primary structure of a known protein.¹²⁹ In a relatively short time frame, the typical investigator would have been able to ascertain which amino acid substitutions could be tolerated at a preselected site in the native sequence.¹³⁰ Producing a mutant having the same activity and overall conformation as the native protein but which differed through one or more conservative changes in the primary structure could arguably have been accomplished with nothing more than routine amounts of experimentation.

An assessment of the "obviousness" of such a species is of course debatable,¹³¹ but in view of the fact that the result of the change imparted

127. It is likely that the prior art showed recombinant expression of the native sequence protein at the time of the patent grant. This is because elucidation of the protein's primary structure is a necessary prerequisite to both recombinant expression of the native sequence and the non-native mutants. Furthermore, the typical progression in research is to successfully express the native sequence before attempting to create novel mutants derived from that native sequence.

128. See *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990) (en banc).

129. In fact, a common use of site directed mutagenesis is to ascertain structural information about the protein by assessing the sensitivity of the native sequence at particular residues to changes. See Bowie, *supra* note 42, at 1306 (proteins are surprisingly tolerant of amino acid substitutions); DeGrado, *supra* note 117, at 622 (site-directed mutagenesis is standard technique for determining which residues in a protein are essential for folding or function).

130. See, e.g., Leatherbarrow & Fersht, *supra* note 33, at 8.

131. Invariably, a debate over whether such a mutant would have been "obvious to try" rather than obvious will arise. The patentee wishing to pursue this line of reasoning

no new activities or properties to the protein, that the method used to impart the change was well known and within the ordinary level of skill in this art, and that in the course of study of the protein, such species would be produced, it is hard to justify a conclusion that a nominally changed protein would have been nonobvious.

The source of this view is the notion of "structural obviousness" based upon similarities of one chemical species to a homolog or analog of that species. The relationship between conservatively substituted species of a known polypeptide sequence and the sequence from which they derive justifies treating these species as "homologs" in the context of assessing the patentability of each species. It may be helpful to consider the "structural obviousness" standard a first screen for the different species encompassed by the hypothetical claim. In light of the recent decision of the Federal Circuit sitting en banc in *In re Dillon*,¹³² structural obviousness is by no means a dormant or out-of-date concept. In *Dillon*, the Federal Circuit summarized the concept of structural obviousness as follows:

In brief, the cases establish that if an examiner considers that he has found prior art close enough to the claimed invention to give one skilled in the relevant chemical art the motivation to make close relatives (homologs, analogs, isomers, etc.) of the prior art compound(s), then there arises what has been called a presumption of obviousness or a prima facie case of obviousness. . . . The burden then shifts to the applicant, who then can present arguments and/or data to show that what appears to be obvious, is not in fact that, when the invention is looked at as a whole. . . . The cases of *Hass* and *Henze* established the rule that, unless an applicant showed that the prior art compound lacked the property or advantage asserted for the claimed compound, the presumption of unpatentability was not overcome.¹³³

In essence, the structural obviousness standard requires that "to be patentable, novel members of a homologous series of (chemical) compounds must possess some nonobvious or unexpected beneficial properties not possessed by a homologous compound disclosed in the prior art."¹³⁴ What satisfies this "unexpected beneficial property" requirement varies depending on the facts of the situation. The predecessor court to the Federal Circuit noted, however, that

in the context of a broad hypothetical claim, however, will not be able to rely upon the benefits of the particular changes made by the patentee or the accused infringer in bolstering such an assertion. See *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988) (holding that unpredictability in the field does not automatically relegate any effort of the ordinary worker to the "obvious to try," rather than obvious standard).

132. 919 F.2d at 692 (reaffirming that structural similarity between claimed and prior art subject matter creates a prima facie case of obviousness where the prior art gives reason or motivation to make the claimed compositions).

133. *Id.* at 696 (citations omitted).

134. *In re Hass*, 141 F.2d 127, 129 (C.C.P.A. 1944).

[p]atentability is not resolved conclusively even where unexpected or nonobvious beneficial properties are established to exist in novel members of a homologous series over prior art members, as the circumstances of the case may require a consideration of other factors. A mere difference in degree is not the marked superiority which ordinarily will remove the unpatentability of adjacent homologs of old substances. The reason for the rule is that the characteristics normally possessed by members of a homologous series are principally the same, and vary but gradually from member to member. Chemists knowing the properties of one member of a series would in general know what to expect in adjacent members.¹³⁵

Biological activity of the compound in question, or its homologs, is often a controversial "unexpected beneficial property," at least to the degree that the species to which it is being compared as an analog lacks the particular activity or function. In one context, the courts have viewed the possession of a particular biological activity as being an expected property of the homolog.¹³⁶ When, however, a new or modified activity is induced or first identified in the homolog, the courts have been reluctant to sustain a *prima facie* obvious holding.¹³⁷ The possession of a *patentably distinct* biological function seems to take the new species out of the realm of "structurally obvious" homologs or analogs.

(b) *Unpredictability and Unexpected Results: The Foil of Structural Obviousness*

The presence of unexpected results, or unpredictability in the art is a complementary issue to "structural obviousness" for homologs. In the context of changing specific amino acid sites in polypeptide sequences to achieve a specific result, this argument may carry some weight.¹³⁸ This conclusion is based upon three assumptions; first, that the prior art at the time of the patent grant most likely did not disclose information

135. *In re Henze*, 181 F.2d 196, 201 (C.C.P.A. 1950) (citations omitted).

136. See, e.g., *In re Merck*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) (claimed drug was obvious in light of structurally similar prior art drug with similar antidepressant properties); *In re Wood*, 582 F.2d 638, 644 (C.C.P.A. 1978) (structural similarity would have led one skilled in the art to expect anti-microbial properties of prior art compound to appear in claimed compound); *In re Mod*, 408 F.2d 1055, 1059 (C.C.P.A. 1969) (anti-microbial activity discovered in claimed compound insufficient to distinguish it from structurally similar prior art compound having other properties in common with it).

137. See, e.g., *In re Schechter*, 205 F.2d 185, 191 (C.C.P.A. 1953) (claimed synthetic analogs possessing commercial advantages over natural insecticides were not obvious).

138. See *Leatherbarrow & Fersch*, *supra* note 33, at 8 ("It is clear, however, that in the absence of structural data on a protein, interpretation of the effects of sequence alteration is often at best difficult and at worst impossible."). In the same issue of *PROTEIN ENGINEERING*, Wetzel states in the context of discussing applications of deduced primary sequence relationships: "Of course, while the effect of such a 'primary sequence element' on a particular property (target site, stability, etc.) may be predictable, the effect of the element on the active conformation of the protein is unpredictable; for example, one may succeed in making an inactive, oxidatively stable mutant." Wetzel, *supra* note 36, at 3.

concerning the relationship between structure and function of the protein; second, that there is an absence of motivation to make the specific change that was made in the accused mutant species; and finally, that there is some non-trivial impact arising from the specific change made. A persuasive argument can be made that while production of the specific mutant species might have been within the abilities of the ordinary worker, the prior art failed to teach that the particular species having the *novel functional characteristics* of the new species could be produced. The result of this unpredictability element, then, is that production of the species would have been merely "obvious to try," rather than obvious.¹³⁹

The "obvious to try" argument generally focuses on the absence of any suggestion in the prior art to produce the exact species contemplated. In essence, the argument serves to counter a conclusion of obviousness for particular inventions in which unusual or unpredictable factors were significant, even though actual reduction to practice of the invention may have required only routine efforts of the ordinary worker in the art. The argument that the invention would have been obvious is thus rejected because it improperly relies on hindsight in evaluating the contribution of the invention.¹⁴⁰ The patentee must be careful in using this type of an argument to support a bare contention that the hypothetically claimed species would have been patentable over the prior art simply because the modification would have been "unpredictable" in its effect without further justification. Recent decisions of the Federal Circuit have emphasized that a certain degree of unpredictability in the art does not automatically render production of any species in that technology merely

139. The Federal Circuit addressed the issue of the "obvious to try" standard in the context of expression of a particular protein in bacterial cells in *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). The court pointed out that this argument does not apply to every attempt in an art which has a certain level of unpredictability. Instead, the court identified two basic types of "obvious to try" situations:

The admonition that "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. . . . In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Id. at 903.

In the context of a specific mutation made to produce a mutant having some desirable and novel characteristic, the argument that it would have been at best obvious to try to make the mutant is persuasive. This is so because it fits into the analysis that (a) general procedures were known in the art that could produce the mutant, but (b) there was no specific direction available to produce the "successful result" (e.g., the new mutant having the unique activity or function). A detailed discussion of the "obvious to try" doctrine is outside the scope of this paper.

140. See *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988); *Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 1380 (Fed. Cir. 1986).

"obvious to try" rather than actually obvious.¹⁴¹ Instead, the patentee should focus an "obvious to try" argument on the elements present in the hypothetical claim, and on the impact these structural elements have on any novel functions or activities derived from the change.¹⁴² Resort to this argument, therefore, requires a specific, rather than generalized, argument that the result obtained is significant.

V. CONCLUSION

The limiting effect of the prior art on expansion of protein patent rights through the doctrine of equivalents, as embodied by the new "hypothetical claim" test, will not present an insurmountable burden for a patentee holding an early protein patent.¹⁴³ This "second burden of proof" should prove to be minimal where, as is typical for most early "purified protein" and recombinant native sequence protein patents, the patentee obtained the patent due to the absence of a significant amount of prior art. The "quasi-pioneering" stature that these early patents enjoy serves to relieve the patentee of a potentially difficult burden.

As protein engineering technology matures, the burden of proving that a new protein mutant as embodied by a "hypothetical claim" is not only a structural and functional equivalent to the assertedly infringing protein, but also that the prior art should not be construed to hold that "hypothetically claimed" protein unpatentable, will become significant. This burden will be especially significant when the patentee holds a patent limited to a specific, non-naturally occurring protein sequence, and there has been substantial activity in the prior art. As discussed at length above, even constructing an appropriate hypothetical claim in such situations will be a difficult task, especially in view of the complex interplay between structural obviousness and "obvious to try" theories for efforts undertaken in the realm of protein engineering.

This summary is not intended to suggest that holders of early protein patents will not face substantial barriers to expanding protein patent rights through the doctrine of equivalents. The burden of proof created by *Wilson Sporting Goods* arises only after factual equivalence between the claimed protein and the accused species has been established by the patentee. Proof of factual equivalence between a naturally

141. See *In re O'Farrell*, 853 F.2d at 903, (possibility of unexpected results provides objective basis for showing invention is nonobvious); *In re Merck*, 800 F.2d at 1097 (obviousness requires only a reasonable expectation that the beneficial result will be achieved).

142. For example, improved resistance to oxidation, increased retention time in the host after administration, omission of a particular functional domain, decreased activity relative to the native species, or additional functional properties.

143. The Federal Circuit applied the hypothetical claim test almost as an afterthought in *Instafoam Prods. v. Universal Foam Sys.*, 906 F.2d 698, 704 (Fed. Cir. 1990).

occurring protein and an even moderately altered derivative is the most significant burden for the patentee to bear in an infringement through equivalence proceeding because of the inherent complexities of protein conformation and function. As the protein engineering field matures, patentees holding such protein patents, or seeking to expand patent rights to novel protein derivatives, will begin to find that the combined effect of these two burdens of proof will be formidable. This burden, however, will help ensure that the doctrine of equivalents will retain the role it was designed to serve: namely, as a means for preventing, through equity, the "piracy" of an applicant's patented invention.