

A CASE FOR EXPANSIVE PATENT PROTECTION OF BIOTECHNOLOGY INVENTIONS

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INTRODUCTION

The United States Patent and Trademark Office and the federal courts are struggling to interpret biotechnology patent claims. Deciding the scope of patent protection for biotechnology inventions¹ is a difficult task and has led to conflicting precedent, as illustrated by *Scripps Clinic & Research Foundation v. Genentech, Inc.* ("Scripps"),² *Hormone Research Foundation v. Genentech, Inc.* ("Hormone Research"),³ and *Genentech, Inc. v. Wellcome Foundation* ("Genentech").⁴ In fact, *Hormone Research* and *Genentech* even reflect uncertainty regarding application of

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1. Although there are several definitions of the term, "biotechnology" is usually taken to mean recombinant DNA techniques and related processes and products, and the production of monoclonal antibodies and related materials and methods. Kate H. Murashige, *Section 102/103 Issues in Biotechnology Patent Prosecution*, 16 A.I.P.L.A. Q.J. 294, 295 (1988). For a concise overview of recombinant DNA technology, see *In re O'Farrell*, 853 F.2d 894, 895-99 (Fed. Cir. 1988). For a more detailed treatment of the subject, see JAMES D. WATSON ET AL., *RECOMBINANT DNA* 63-133 (2d ed. 1992). For a summary of monoclonal antibody techniques, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1368-70 (Fed. Cir. 1986). See also *In re Wands*, 858 F.2d 731, 733-34 (Fed. Cir. 1988); LUBERT STRYER, *BIOCHEMISTRY* 895-97 (3d ed. 1988).

2. 666 F. Supp. 1379 (N.D. Cal. 1987), *modified*, 678 F. Supp. 1429 (N.D. Cal. 1988), *summary judgment granted*, 707 F. Supp. 1547 (N.D. Cal. 1989), *aff'd in part, rev'd in part, vacated in part, and remanded*, 927 F.2d 1565 (Fed. Cir.), *clarified*, 18 U.S.P.Q.2d (BNA) 1896 (Fed. Cir.), *reh'g denied*, Nos. 89-1541, 89-1542, 89-1543, 89-1646 & 89-1647, 1991 U.S. App. LEXIS 8701 (Fed. Cir. Apr. 30, 1991); see also *Scripps Clinic & Research Found., Inc. v. Baxter Travenol Lab., Inc.*, 729 F. Supp. 1473 (D. Del. 1990); *Scripps Clinic & Research Found., Inc. v. Baxter Travenol Lab., Inc.* 17 U.S.P.Q.2d (BNA) 1046 (D. Del. 1990) (related cases).

3. 708 F. Supp. 1096 (N.D. Cal. 1988), *aff'd in part, vacated in part, and remanded*, 904 F.2d 1558 (Fed. Cir.), *reh'g denied*, Nos. 89-1082 & 89-1111, 1990 U.S. App. LEXIS 17559 (Fed. Cir. Sept. 24, 1990).

4. 14 U.S.P.Q.2d (BNA) 1363 (D. Del. 1990).

two basic patent law doctrines: the doctrine of literal infringement and the reverse doctrine of equivalents.⁵

Biotechnology claim interpretation is difficult for at least three reasons. First, biotechnology itself is an intimidating amalgamation of biology and chemistry. Second, biotechnology claim interpretation forces a judge, jury, or patent examiner to grapple with rather fundamental issues such as the significance of the term "human" in describing a protein. And third, it raises important policy questions. For example, what type of "legal monopoly" should be granted to an innovator whose significant contribution to the public welfare can be diminished quickly by a competitor's development of an improved product or technique?

In this Article, we maintain that the interpretation of biotechnology patent claims need not be obfuscated by the abstruse subject matter. Instead, the process of claim construction can be assisted by borrowing established principles from inorganic polymer patent law. We conclude that adherence to chemical patent law precedent, coupled with an understanding that biotechnology should be viewed legally as a blend of biology and chemistry, leads to the correct level of patent protection for biotechnology inventions.

I. THE INSTRUCTIVE PRECEDENT OF POLYMER CASES

Most biotechnology products developed to date, including those in *Scrapps*, *Hormone Research*, and *Genentech*, are human enzymatic proteins.⁶ These proteins can be obtained in two ways. They can be

5. "The determination of whether a patent claim has been literally infringed involves two inquiries: whether the claims have been properly interpreted to determine their scope, and whether each limitation of the properly construed claims is found in the accused product or process." *Hormone Research*, 904 F.2d at 1562 (citations omitted).

"Infringement under the doctrine of equivalents is an equitable doctrine intended, 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." *Id.* at 1564 (citation omitted). To infringe under the doctrine of equivalents, an accused product or process must perform substantially the same function in substantially the same way to obtain the same result. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608-09 (1950); see *Wilson Sporting Goods Co. v. David Geoffrey & Assocs.*, 904 F.2d 677, 684 (Fed. Cir. 1990) ("the doctrine of equivalents does not involve expansion of the claims . . . [but] expands the right to exclude 'equivalents' of what is claimed") (citations omitted); see also Laura A. Handley, *Refining the Graver Tank Analysis With Hypothetical Claims: A Biotechnology Exemplar*, HARV. J.L. & TECH., Fall 1991 at 31.

6. "Proteins are large polymeric molecules consisting of chains of smaller building

manufactured by either recombinant or synthetic means, or they can be extracted in the purification of naturally-occurring materials.⁷

These proteins are complex biological polymers whose behavior at the molecular level is often not completely understood.⁸ When construing patent claims involving these complex proteins, courts should look to the broad rights granted patent holders in inorganic polymer cases like *Phillips Petroleum Co. v. United States Steel Corp.* ("Phillips")⁹ and *Studiengesellschaft Kohle v. Dart Industries* ("Kohle").¹⁰

A. Kohle's and Phillips's Infringement Analysis

In *Kohle*, the plaintiff claimed a method of making olefins using a novel catalyst comprised of an organic aluminum component, preferably diethylaluminum chloride ("DEAC"), and a halogen, typically titanium chloride. Defendant Dart conceded that its catalyst contained DEAC but argued that it used a type of titanium chloride having "sufficient quantitative and qualitative distinctions" from the halogen disclosed in the plaintiff's patent. Stressing this difference in halogens, the defendant maintained that its catalyst was outside the scope of the plaintiff's patent claims and, consequently, did not infringe the patent literally.¹¹

The court did not accept the defendant's position. There was no dispute that the broad claims at issue encompassed DEAC and various

blocks, called amino acids, that are linked together covalently." *In re O'Farrell*, 853 F.2d 894, 896 (Fed. Cir. 1988). "It is the exact sequence in which the twenty types of amino acids are strung together in a polypeptide chain that determines the identity of a protein and its chemical characteristics." *Id.* In turn, it is the sequencing of the four nucleotides (adenine, guanine, cytosine, and uracil) along chromosomal DNA that ultimately determines protein amino acid sequence, and protein structure and function. See WATSON, ET AL. *supra* note 1, at ch. 3; STRYER, *supra* note 1, at 23-24.

7. For a description of the use of recombinant DNA technology to make a specific protein, see *Amgen, Inc. v. Chugai Pharmaceutical Co.*, U.S.P.Q.2d (BNA) 1737, 1742-45 (D. Mass. 1989), *aff'd in part, rev'd in part, vacated in part*, 927 F.2d 1200 (Fed. Cir. 1991). See also *In re O'Farrell*, 853 F.2d at 898-99; STRYER, *supra* note 1, at 130-38.

Proteins can be synthesized using solid phase methods, i.e. step-by-step amino acid addition. See *Hormone Research*, 708 F. Supp. at 1098; STRYER, *supra* note 1, at 64-67. Naturally occurring proteins can be isolated and purified from a natural source (e.g., plasma) by adsorbing the proteins onto monoclonal antibodies specific to the protein. See *Scripps*, 666 F. Supp. at 1383; STRYER, *supra* note 1, at 62-64.

8. See, e.g., *In re O'Farrell*, 853 F.2d at 898-99.

9. 673 F. Supp. 1278 (D. Del. 1987), *aff'd*, 865 F.2d 1247 (Fed. Cir. 1989).

10. 216 U.S.P.Q. (BNA) 381 (D. Del. 1982), *aff'd*, 220 U.S.P.Q. 841 (Fed. Cir. 1984), *on remand*, 4 U.S.P.Q.2d (BNA) 1817 (D. Del. 1987), *aff'd*, 9 U.S.P.Q.2d (BNA) 1273 (Fed. Cir. 1988).

11. *Kohle*, 216 U.S.P.Q. (BNA) at 401-02.

species of titanium chloride. Consequently, applying these claims to Dart's catalyst was easy since the catalyst fell squarely within the language of the claim. With literal infringement established, Dart had to argue that it was not liable under the reverse doctrine of equivalents.¹² Despite finding that Dart's catalyst substantially improved activity and possessed compositional differences, the *Kohle* court concluded that the "functional similarity" and the similar chemistry of Dart's catalyst put Dart's process within the literal scope of the plaintiff's claims.¹³

Phillips dealt with the following claim:

Normally solid polypropylene, consisting essentially of recurring propylene units, having a substantial crystalline polypropylene content. . . .¹⁴

There was no dispute about the meaning of any term of this claim, and the defendants conceded that their crystalline polypropylene products fell within the claim's literal scope.¹⁵ But like their counterparts in *Kohle*, the *Phillips* defendants maintained that they avoided infringement under the reverse doctrine of equivalents.¹⁶

To rule on the issue of non-infringement under the reverse doctrine of equivalents, however, the district court in *Phillips* looked to the "principle" or essence of the invention,¹⁷ and it determined that this essence was crystalline polypropylene.¹⁸ The defendants did not attempt to prove that their products differed in principle from crystalline polypropylene.¹⁹ Instead, they relied on differences in molecular weight, toughness, and commercial utility to distinguish their products.²⁰ The court rejected this evidence as insufficient to sustain a finding of non-infringement under the reverse doctrine of equivalents. It found that the

12. See *supra* note 5. As *Kohle* and *Phillips* illustrate, the reverse doctrine of equivalents is treated with healthy skepticism by the courts and is rarely successful. See *SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1123 n.19 (Fed. Cir. 1985); *Phillips*, 673 F. Supp. at 1350; see also *Handley, supra* note 5, at 40-41.

13. 216 U.S.P.Q. (BNA) at 405.

14. *Phillips*, 673 F. Supp. at 1286.

15. *Id.* at 1345-46.

16. *Id.* at 1350.

17. *Id.* at 1354.

18. *Id.*

19. *Id.* at 1353.

20. *Id.* at 1350-54.

defendants' argument misconstrued this judicial doctrine and that they infringed the plaintiff's patent.²¹

The Federal Circuit affirmed the trial court's rejection of the defendants' efforts to distinguish their products as superior compositions.²² The Federal Circuit also endorsed looking to the "principle" of the invention, explaining that a "principle"-based standard avoids the difficulties of applying a "method-like" test (functioning in a substantially different way)²³ to a composition.

B. *Protecting the Principle of the Claimed Invention*

Kohle and *Phillips* are noteworthy for rejecting arguments that literal infringement can be escaped by making modifications or improvements which still fall within the language of the patent claims. Both cases establish that where complex, macromolecular chemical compositions are involved, any effort to avoid literal infringement under the reverse doctrine of equivalents must demonstrate that the allegedly infringing product differs in principle from the claimed composition.²⁴ This "in principle" standard is just as challenging for biological subject matter as it is for inorganic polymers.

II. INFRINGEMENT OF BIOTECHNOLOGY PATENT CLAIMS

A. *Genentech's and Hormone Research's Struggle with Claim Interpretation*

Genentech involved recombinantly-derived glycoprotein tissue plasminogen activator ("t-PA"), a 527 amino-acid-enzyme crucial to the human clotting process.²⁵ Defendants manufactured met-t-PA and

21. *Id.* at 1353-54.

22. 865 F.2d at 1253. Significantly, the Federal Circuit stressed that plaintiff's claim did not fail to satisfy the enablement requirement of 35 U.S.C. § 112, ¶ 1 (1988), merely because it failed to disclose defendants' commercially superior embodiments. *Id.* at 1250-52.

23. *Kohle*, 216 U.S.P.Q. (BNA) at 405.

24. *Phillips*, 673 F. Supp. at 1353.

25. The enzyme t-PA converts (inactive) plasminogen circulating in the bloodstream to (active) plasmin, a proteolytic enzyme which breaks down bonds between clot-forming fibrin molecules. *Genentech*, 14 U.S.P.Q.2d (BNA) at 1365.

FE1X, synthetic variants of recombinant t-PA which the plaintiff alleged infringed the claims of its U.S. Patent Nos. 4,752,603 ("'603 Patent") and 4,766,075 ("'075 Patent").²⁶ The broadest claim of the '603 Patent read as follows:

Human plasminogen activator, having thrombolytic properties, immunologically distinct from urokinase and having a specific activity of about 500,000 IU/mg. using the WHO First International Reference Preparation of t-PA (tissue plasminogen activator) as assay standard or a specific activity of about 90,000 IU/mg. using the WHO First International Reference Preparation of urokinase as assay standard.²⁷

Genentech's '075 Patent claimed an isolate consisting of the DNA sequence encoding human t-PA. The '075 Patent also claimed a related expression vector and transformed cell culture.²⁸

The met-t-PA product differed in amino acid sequence from naturally occurring t-PA solely in the substitution of methionine for valine at the 245 amino acid position, an enzymatically-active region of the protein.²⁹ This substitution caused met-t-PA to have one less glycosylation site as a location for carbohydrate linkage.³⁰ The amino acid sequence of the

26. *Id.* at 1365-66. Defendant's recombinant manufacture of t-PA took place in the United Kingdom and therefore did not infringe the '075 Patent. *Id.* at 1365.

27. *Id.* at 1367. "Specific activity" refers to the number of units of activity for a given mass of protein. *Scripps*, 927 F.2d at 1569 n.4.

28. For example, claims 1-3 of the '075 Patent read as follows:

1. A DNA isolate consisting essentially of DNA sequence encoding human tissue plasminogen activator;
2. A recombinant expression vector containing a DNA sequence encoding human tissue plasminogen activator, wherein the vector is capable of expressing human tissue plasminogen activator in a transformed microorganism or cell culture; and
3. A cell culture capable of expressing human tissue plasminogen activator, obtained by transforming a mammalian cell line with a vector according to claim 3 [sic].

Genentech, 14 U.S.P.Q.2d (BNA) at 1367.

29. The met-t-PA substitution took place in the Kringle 1 ("K1") domain that acts on plasminogen circulating in the bloodstream, *id.* at 1368, and was apparently due to a cloning error. See Mark Ratner, *T-PA Trials, Tribulations, and Litigation*, 8 *BIO/TECHNOLOGY* 385 (1990).

30. *Genentech*, 14 U.S.P.Q.2d (BNA) at 1368.

FE1X product differed from natural t-PA in the deletion of the eighty-one amino acid-long F and E domains. The F domain allows t-PA to bind to fibrin, a clot-forming protein fiber.³¹

The meaning of Genentech's claims, particularly the significance of the term "human" in describing t-PA, was vigorously contested by the parties in their motions for summary judgment on the issue of infringement. Plaintiff Genentech characterized the claimed t-PA as encompassing compositions that (a) converted plasminogen to plasmin, (b) attached to fibrin, and (c) exhibited the immunological properties of t-PA.³² Predictably, the defendants took a narrower view of the claim's scope. They argued that the claims were limited to t-PA having the precise characteristics of human t-PA and its naturally occurring allelic variations.³³ The *Genentech* court agreed with the defendant's narrow interpretation.³⁴

In its motion for summary judgment, Genentech attempted to prove that the defendants' met-t-PA or FE1X products were naturally-occurring allelic variants of human t-PA and that the defendants' products satisfied the specific activity claim limitation.³⁵ Genentech failed on both counts. Summary judgment of no literal infringement was entered in favor of defendants, and Genentech was left to prove infringement under the doctrine of equivalents.

While the *Genentech* court was persuaded that FE1X and met-t-PA had the same intended result and function as plaintiff's t-PA, summary judgment of infringement under the doctrine of equivalents was precluded because material questions of fact existed as to whether those three compositions cleaved plasminogen in substantially the same way. To answer these questions, the jury had to consider whether FE1X bound to fibrin in the same way as human t-PA and whether the met-t-PA 245 amino acid substitution affected secondary and tertiary structure enough to alter the method of cleavage.³⁶ Ultimately, the jury found that both the met-t-PA and FE1X infringed under the doctrine of equivalents.³⁷

In *Hormone Research*, the plaintiff suffered a fate similar to that of the plaintiff in *Genentech* by losing on the threshold issue of claim interpreta-

31. *Id.* at 1365.

32. *Id.* at 1368.

33. *Id.*

34. *Id.*

35. *Id.* at 1369-70.

36. *Id.* at 1370-71.

37. Judgment, *Genentech* (Doc. No. 408).

tion. The patent claim at issue in *Hormone Research* contained two mistakes. First, it misstated the number of amino acids in human growth hormone ("HGH") as 190 instead of the actual 192. And second, the patentee confused the amino acids at positions 73, 106, and 108,³⁸ and then claimed synthetic HGH by reference to a figure ("Figure 2") depicting this errant sequence.³⁹ Defendant Genentech produced two allegedly-infringing HGH products. One had the same amino acid sequence as natural HGH. The other differed from natural HGH because it contained an additional methionine at the amino terminus.⁴⁰

The district court in *Hormone Research* rejected plaintiff's argument of literal infringement. The court interpreted "corresponding to Figure 2" in the plaintiff's composition claims as an amino acid sequence identical to that of Figure 2.⁴¹ Given this claim construction, Hormone Research pursued its literal infringement case by arguing that the sequence differences between the accused products and the claimed figure were inconsequential.⁴² The district court, however, judged Hormone Research's assertion to be disingenuous because the defendant used amino acids that were structurally distinct from the corresponding amino acids claimed by Hormone Research.⁴³

Like the plaintiff in *Genentech*, the plaintiff in *Hormone Research* was forced to prove infringement under the doctrine of equivalents. But the prosecution history of its patent prevented Hormone Research from pursuing such a claim. During the previous prosecution of a dependent claim not at issue in this case, Hormone Research successfully distinguished a prior art reference by arguing that the claim in the prior art was

38. *Hormone Research*, 708 F. Supp. at 1098. The patentee identified glutamic acid rather than glutamine at position 73; aspartic acid rather than asparagine at position 106; and asparagine rather than aspartic acid at position 108. *Id.*

39. Composition claim 12 of U.S. Patent No. 3,853,833 ("'833 Patent") (assigned to Hormone Research) read as follows:

A composition of matter consisting essentially of a synthetic, biologically active substance which has a structure corresponding to FIG. 2 of the accompanying drawing.

Hormone Research, 904 F.2d at 1561 (emphasis added). Method claims directed towards production of synthetic HGH by formation of an amino acid chain in the sequence of natural HGH, or the errant Figure 2, were also at issue. *Id.*

40. *Hormone Research*, 708 F. Supp. at 1098-99 n.1.

41. *Id.* at 1101.

42. *Id.*

43. *Id.*

limited to the structure of Figure 2.⁴⁴ Thus, the district court concluded that file wrapper estoppel prevented Hormone Research from now maintaining that defendant's product was within the scope of its claims.⁴⁵

Although the Federal Circuit affirmed the district court's finding of no literal infringement, it did so on other grounds. According to the Federal Circuit, in construing the meaning of the term "corresponding to Figure 2," the district court should have looked no further than the prosecution history of the patent, where plaintiff's remarks plainly indicated that "corresponding" meant "identical."⁴⁶ However, the Federal Circuit remanded the issue of prosecution history estoppel to the district court because it was uncertain what Hormone Research relinquished during patent prosecution. Drawing all inferences in Hormone Research's favor, the appellate court stated that the claims at issue might have been limited to the Figure 2 structure to distinguish cited prior art (a clear estoppel). Alternatively, Hormone Research might have intended to distinguish its composition from the cited art by limiting its patent claims to synthetic products or by arguing that the cited art did not disclose how to make the claimed invention. No estoppel would arise from either of those two latter arguments.⁴⁷

B. Scripps's Focus on Material Structure and Function

Scripps involved Human Factor VIII:C, a 2,332 amino acid enzymatic protein critical to the blood clotting process.⁴⁸ Scripps's U.S. Reissue Patent No. RE 32,011 ("R'011 Patent") contained both product-by-process and product claims to Factor VIII:C as illustrated by the following claims:

13. Highly purified and concentrated human or porcine VIII:C prepared in accordance with the method of claim 1.

44. *Id.* at 1105.

45. *Id.* at 1106.

46. *Hormone Research*, 904 F.2d at 1563.

47. *Id.* at 1566-67.

48. *Scripps*, 666 F. Supp. at 1383-84. Factor VIII:C is essential to a complex series of interactions between blood proteins which forms a platelet-adhering, fibrin network. *Id.* The R'011 Patent also contained method claims directed towards Scripps's Factor VIII:C separation technique, discussed *infra*.

24. A human VIII:C preparation having a potency in the range of 134 to 1172 units per ml and being substantially free of VIII:RP.⁴⁹

Scripps's method incorporated in claim 13 involved purification of Factor VIII:C from human or porcine plasma. This process involved two steps. First, the naturally occurring Factor VIII:C-Factor VIII:RP complex⁵⁰ is adsorbed onto monoclonal antibodies specific to the complex, and second, the desired Factor VIII:C is extracted from the adsorbed complex by washing with a salt solution.⁵¹ However, while suitable plasma sources for Scripps's method were limited,⁵² sources for Genentech's later-developed recombinant technique were not. Thus, Genentech's recombinant technology "broke new ground" in its ability both to isolate the DNA sequence encoding Factor VIII:C and to produce that very large protein.⁵³

Scripps sued Genentech for infringement of both the product-by-process and product claims of the R'011 Patent and moved for summary judgment on the issue of infringement. In deciding that motion, the district court construed the product-by-process claims as limited to Factor VIII:C made by the process described in those claims.⁵⁴ Genentech's recombinantly derived Factor VIII was not made by the process recited in Scripps's product-by-process claims and was found not to infringe them.⁵⁵

The district court also rejected suggestions to limit the scope of Scripps's patent by either reading a process limitation from other claims

49. Factor VIII:RP is a related protein known as the von Willebrand Factor. *Id.* at 1383.

50. *Id.*

51. *Id.* at 1383-84.

52. *Id.*

53. *Id.* at 1384. Under this construction, only one of the product-by-process claims (claim 13) of the R'011 Patent was held literally infringed as a result of Genentech's work to determine the Factor VIII:C amino acid sequence. *Id.* at 1389.

54. *Id.* at 1386-87.

55. *Id.* at 1388-89. A product-by-process claim "usually appears when the invention is a chemical or biological product of such structural complexity that the product can be defined in independent structural terms. The premise of such claims has been called the Rule of Necessity, for it provides a way of patenting inventions or discoveries whose structure is not sufficiently known or knowable to be described objectively." *Atlantic Thermoplastics Co. v. Faytex Corp.*, 974 F.2d 1279, 1282 (Fed. Cir. 1992) (Newman, J., dissenting).

of the R'011 Patent into the product claims, or limiting the product claims to the embodiments disclosed in the specification.⁵⁶ The patent's prosecution history also worked against Genentech's attempt to limit the product claims:

The prosecution history thus makes clear that both Scripps and the examiner considered the term "human Factor VIII:C" to be descriptive not of its derivation from human plasma but of its fundamental characteristics peculiar to the species Human Factor VIII:C as claimed in the patent therefore applies to any Factor VIII:C preparation, regardless of how produced, having the same material structural and functional characteristics as the plasma-derived preparation.⁵⁷

The defendant introduced evidence that the recombinant product did not exhibit natural amino acid sequence variation and was free of human viruses. Other evidence suggested that the defendant's product might vary in carbohydrate content from the patented one.⁵⁸ However, the court decided that none of these differences sufficiently demonstrated that Genentech's recombinant product was structurally or functionally different from Scripps's claimed Factor VIII:C.⁵⁹ Therefore, Genentech was found to have literally infringed Scripps's patent.

On appeal, the Federal Circuit reversed the finding of infringement of Scripps's product claim and directed the district court to consider whether Genentech's recombinant product was so changed "in principle" as to avoid literal infringement under the reverse doctrine of equivalents.⁶⁰ The circuit court also noted a contradiction in Genentech's argument that the R'011 Patent's product claims should have been limited to Scripps's method despite Genentech's acknowledgement that the Factor VIII:C product claims were proper.⁶¹ The Federal Circuit also held that in construing product-by-process claims for both validity and infringement, such claims are not limited to products prepared by the process set forth

56. *Id.*

57. *Id.* at 1390.

58. *Id.* at 1393-94.

59. *Id.*

60. *Scripps*, 927 F.2d at 1580-81. A Scripps witness testified that the stability and formulation of the purified and recombinant products differed, and Genentech claimed that there were differences in specific activities and purities.

61. *Id.*

in the claims. The issue of Genentech's infringement of the R'011 Patent's product-by-process claims was therefore also remanded to the district court.⁶²

III. INTERPRETING *SCRIPPS*, *GENENTECH*, AND *HORMONE RESEARCH*

A. *Limiting the Precedential Value of Genentech and Hormone Research*

Genentech and *Hormone Research* do not mean that literal infringement of a protein patent claim can be avoided simply by minor variation of a claimed amino acid sequence. Polymer patent law is particularly instructive on this point. *Kohle* and *Phillips* establish that insubstantial changes to a claimed complex chemical composition, which do not materially alter its structure or function, still constitute literal infringement. Thus the reverse doctrine of equivalents does not bar infringement if the altered compound falls within the literal scope of the claim at issue.⁶³

Genentech and *Hormone Research* may be limited by attention to their specific facts. *Genentech* was remanded because the plaintiff could not offer evidence on a key claim limitation (specific activity) in its motion for summary judgment on the grounds of literal infringement.⁶⁴ Admittedly, the *Genentech* court based its conclusion that met-t-PA did not literally infringe at least partly on a finding that defendants' "single amino acid substitution . . . produces a t-PA that is not the human t-PA as claimed in the patent or a naturally occurring allelic variant"⁶⁵ Since that finding was made on a motion for summary judgment, and in the absence of any proof that met-t-PA could occur naturally and therefore be considered as the claimed "human t-PA," its outcome does

62. *Id.* at 1583-84. Unfortunately, the court's treatment of product-by-process claims is, itself, in conflict. A later panel of the Federal Circuit disagreed with this interpretation of product-by-process claims to technical developments outside the biotechnology field. *Atlantic Thermoplastics Co. v. Faytex Corp.*, 970 F.2d 834 (Fed. Cir. 1992) (involving shock absorbing shoe inner soles).

63. *Kohle*, 216 U.S.P.Q.2d (BNA) at 405; *Phillips*, 673 F. Supp. at 1553-54.

64. 14 U.S.P.Q.2d (BNA) at 1369.

65. *Id.* at 1370.

not invite future claim avoidance by making inconsequential sequence changes.

In *Hormone Research*, prosecution history estoppel prevented the plaintiff from establishing that the defendant's synthetic hormone infringed under the doctrine of equivalents.⁶⁶ Thus, the district court in *Hormone Research* concluded that "in chemical structures as sensitive as these the literal infringement showing must be exacting,"⁶⁷ and the prosecution history of the patent-in-suit left it with little choice but to limit *Hormone Research* to its "Figure 2" protein.

When compared to *Genentech* and *Hormone Research*, *Scripps* demonstrates potential recognition of expansive biotechnology patent claims. Of the three cases, *Scripps* is most in accord with the established precedent of polymer patent cases such as *Phillips*.

B. Similarities Between *Scripps* and *Phillips*

Both *Scripps* and *Phillips* rejected an alleged infringer's argument that although its composition was within the literal scope of the claims at issue, the claims should be more narrowly construed.⁶⁸ The defendants' strategy in *Phillips* (that the scope of the plaintiff's claim had to be limited to polypropylenes having properties set forth in the patent specification)⁶⁹ and that of *Genentech* in *Scripps* (that the Factor VIII product claims were limited to purified natural products)⁷⁰ was to improperly restrict patent claims to the embodiments disclosed by the patentees in their respective specifications.⁷¹

Scripps uncontroverted evidence that *Genentech's* recombinant Factor VIII met each of the limitations of the product claims at issue⁷² should have been dispositive of the literal infringement issue. On the most important of these claim limitations—that the product comprised "human VIII:C"—the *Scripps* court exhaustively considered the defendant's evidence of possible differences in the amino acid sequence and carbohy-

66. 708 F. Supp. at 1106.

67. *Id.* at 1102.

68. *Cf. Scripps*, 927 F.2d at 1580-81; *Scripps*, 666 F. Supp. at 1389-90; *Phillips*, 673 F. Supp. at 1345.

69. 673 F. Supp. at 1345.

70. 666 F. Supp. at 1389-90.

71. *Id.*

72. *Id.* at 1394-95.

drate content of its recombinant product.⁷³ It found that the defendant was attempting to "demonstrate that recombinant Factor VIII:C does not fall within the scope of [the] product claims."⁷⁴ Rather than letting such differences confuse the central issue, which was whether "recombinant VIII:C" was equivalent to the claimed "human VIII:C," the *Scripps* court focused on the structural and functional similarities between recombinant VIII:C and plasma-derived VIII:C. None of the product differences cited by Genentech constituted limitations outside the scope of *Scripps*'s claims.⁷⁵ Thus, the Federal Circuit should not have remanded the question of infringement to the district court.⁷⁶

According to the Federal Circuit, however, potential differences in the specific activities and purities of plasma-derived and recombinantly derived Factor VIII:C mandated consideration of how defendant's recombinant product differed "in principle" from the claimed Factor VIII:C.⁷⁷ No evidence is cited in the district court's opinion, however, to suggest any functional difference in the way recombinant and plasma-derived Factor VIII:C activate proteins during formation of a fibrin network.⁷⁸ *Phillips* is relevant because it makes clear that, at least in the polymer context, qualitative differences alone do not circumvent literal infringement absent proof that the defendant's product functions in a substantially different way and is consequently a different product.⁷⁹

While the *Scripps* remand may have been needless, it need not be useless. The district court has a unique opportunity to embrace *Phillips* in the biotechnology context and force the defendant to establish that its product does not embody the "essence" of the claimed invention⁸⁰ (properly characterized as human Factor VIII having the claimed potency and purity)⁸¹. In the same way that *Phillips* ignored unpersuasive evidence of improved product quality in the polymer area, factors like improved stability, greater specific activities, or increased purities still within the claimed ranges, should be rejected when offered as proof of significant differences in the biotechnology area.

73. *Id.* at 1393-94.

74. *Id.* at 1393.

75. *Id.* at 1393-94.

76. See *Phillips*, 673 F. Supp. at 1354.

77. *Scripps*, 927 F.2d at 1581.

78. See *Scripps*, 666 F. Supp. at 1393-94.

79. 673 F. Supp. at 1357.

80. *Id.* at 1354.

81. *Scripps*, 666 F. Supp. at 1390.

C. *Harmonizing Expansive Biotechnology Patent Protection
with the Statutory Enablement Requirement*

A patentee will frequently have to distinguish a claimed biological composition from its known, naturally-occurring variant on the basis of purity, specific activity, or some other quality.⁸² Once a distinction is established, the claim cannot be construed to cover a composition whose important characteristics differ significantly. "[T]he scope of . . . claims must bear a reasonable correlation to the scope of enablement⁸³ provided by the specification to persons of ordinary skill in the art."⁸⁴

Expansive enforcement of biotechnology patent claims is limited by the statutory enablement requirement which requires that a patent teach an individual of ordinary skill in the art how to make and use the invention.⁸⁵ However, care must be taken so that a biological composition or method does not escape infringement by a change obvious to a person with ordinary skill in the art.⁸⁶ For example, the Federal Circuit in *Scripps* expressly reaffirmed the propriety of "open ended" composition claims (e.g., "a human VIII:C preparation . . . substantially free of VIII:RP")⁸⁷ in the absence of evidence that the alleged differences in specific activities and purities of defendant's product were not enabled by the patent-in-suit.⁸⁸

82. See, e.g., *Ex Parte Stern*, 13 U.S.P.Q.2d (BNA) 1379 (Bd. Pat. App. & Int'l 1989) (examiner's refusal to consider the purity of claimed interleukin 2 as evidence of patentability was clearly erroneous); *Ex Parte Gray*, 10 U.S.P.Q.2d (BNA) 1922 (Bd. Pat. App. & Int'l 1989) (claim to recombinantly produced human nerve growth factor ("NGF"), in the absence of any evidence to the contrary, is unpatentable as obvious over known, purified, naturally-occurring NGF).

83. 35 U.S.C. § 112, ¶ 1 (1988), provides in relevant part that the patent "specification shall contain a written description of the invention . . . as to enable any person skilled in the art . . . to make and use the same"

84. *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) (claimed hormone having a potency of "at least 1" was insufficiently supported under § 112, ¶ 1, by a specification disclosing hormones having a potency of not much greater than 2.3).

85. 35 U.S.C. § 112, ¶ 1 (1988). Handley, *supra* note 5, at 62-63, proposes an infringement test in which the issue of whether a hypothetical claim to a purportedly infringing biological compound is enabled by the patent-in-suit would prove dispositive.

86. See *Ex parte Stern*, 13 U.S.P.Q.2d (BNA) at 1382-83 (no evidence that known heterologous interleukin compositions could not be purified to claimed homogeneous composition using known purification techniques).

87. Such claims "may be supported if there is an inherent, albeit not precisely known, upper limit and the specification enables one of skill in the art to approach that limit." *Scripps*, 927 F.2d at 1572.

88. *Scripps*, 666 F. Supp. at 1390-91.

Amgen, Inc. v. Chugai Pharmaceutical Co. ("Amgen")⁸⁹ indicates that generic patent claims to genetic sequences,⁹⁰ while permissible, will face particular scrutiny as concerns enablement.⁹¹ The district court in *Amgen* relied primarily on evidence of the unpredictable effect of amino acid substitution on erythropoietin ("EPO")⁹² and concluded that a generic claim to all DNA sequences encoding a polypeptide and having an amino acid sequence "sufficiently duplicative" of EPO was not enabled.⁹³ The Federal Circuit affirmed but noted that generic claims to genetic sequences are valid only if commensurate in scope with the disclosed invention.⁹⁴

Any application of the statutory enablement requirement to set the boundaries for biotechnology patent protection is a fact-intensive inquiry whose outcome varies. As techniques in the art, such as DNA sequencing and protein purification, become more routine,⁹⁵ enablement should have diminishing impact on the enforcement of biotechnology claims.⁹⁶

89. 13 U.S.P.Q.2d (BNA) 1737 (D. Mass. 1989), *aff'd in part, rev'd in part, remanded*, 927 F.2d 1200 (Fed. Cir. 1991). Plaintiff Amgen claimed that defendant Genetics Institute ("GI") infringed Amgen's U.S. Patent No. 4,703,008 which claimed purified DNA sequences encoding EPO (a red blood cell-stimulating protein) and related host cells. GI counterclaimed that Amgen's recombinantly-derived rEPO infringed GI's U.S. Patent No. 4,677,195 which claimed purified (naturally-occurring) EPO.

GI did not contest the issue of whether its purified EPO infringed Amgen's claimed rEPO, and Amgen's rEPO was found to infringe GI's claims in a related case. Ultimately, the Federal Circuit affirmed the district court's decision that Amgen's patent claims were valid, enforceable, and infringed with the exception of certain broad sequence claims discussed *infra*. GI's patent claims were held invalid by the Federal Circuit for failure to satisfy the enablement requirement of 35 U.S.C. §112, ¶ 1 (1988).

90. For example, claim 7 of U.S. Patent No. 4,703,008 ("1'008 Patent") at issue in *Amgen* read, in pertinent part, as follows: "a purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin . . ." 13 U.S.P.Q.2d (BNA) at 1741.

91. See also *Handley*, *supra* note 5, at 47.

92. 13 U.S.P.Q.2d (BNA) at 1776.

93. *Id.*

94. 927 F.2d at 1214. Amgen's '008 Patent disclosed how to make and use only a few of the nearly 4,000 possible EPO analogues (altered genes). *Id.* at 1213-14; *Amgen*, 13 U.S.P.Q.2d (BNA) at 1776.

95. See Rebecca S. Eisenberg, *Patenting The Human Genome*, 39 EMORY L.J. 721, 730 (1990); *Handley*, *supra* note 5, at 46 n.94.

96. This is a corollary of the holding in *Ex Parte Stern*, 13 U.S.P.Q.2d (BNA) 1379, 1382-83 (Bd. Pat. App. & Int'f 1989), that an applicant must establish that his claimed subject matter is not the result of applying routine techniques to known material.

IV. PUBLIC POLICY FAVORS EXPANSIVE PATENT PROTECTION

Public policy is advanced by broad biotechnology patent protection because increasing investment in biotechnology products and processes⁹⁷ motivates attempts to secure strong patent claims.⁹⁸ Since further innovation will require great expense and laborious research, investors need reasonable assurances that expansive product or product-by-process patent protection will facilitate attractive returns on investment.⁹⁹ This is particularly true regarding the limited enforcement of process or DNA sequence claims¹⁰⁰ and claims to host cells.¹⁰¹

Scripps directs courts to consider both the patentability and infringement of product-by-process and product claims, without reading inherent process limitations into the latter.¹⁰² Thus, it establishes fair criteria to distinguish the true inventive contribution of those who subsequently enter the market from a prior patent holder's broad composition claim. If, as in *Scripps*, the newcomer's advancement constitutes a novel recombinant synthesis to make an already broadlyclaimed compound, the innovator will be granted a valid method patent claiming the pioneering technique. The company may then sell or license its method to receive a fair return for its contribution.¹⁰³

As illustrated by *Scripps*, giving expansive patent protection to biotechnology inventions need not stifle progress.¹⁰⁴ On the contrary,

97. See Mark D. Dibner, *Tracking Trends in U.S. Biotechnology*, 9 *BIO/TECHNOLOGY* 1334 (1991).

98. See Al Gore, *Planning A New Biotechnology Policy*, *HARV. J.L. & TECH.*, Fall 1991 at 19, 25.

99. See Eisenberg, *supra* note 95, at 736.

100. A competitor, as in *Scripps*, could make recombinantly what the patentee has claimed by way of a purification or synthetic process. As discussed, *Amgen* imposes a fairly strict enablement standard constraining the breadth of DNA sequence claims.

101. *Amgen, Inc. v. United States Int'l Trade Comm'n*, 902 F.2d 1532, 1537-40 (Fed. Cir. 1990) (holding that the importation of a product manufactured abroad using host cells patented in the United States did not violate 19 U.S.C. § 1337(a) (1988) in the absence of any process patent claims because the internal workings of host cells in making a product are not "process" as defined by § 1337). Section 1337 declares unlawful the importation into the United States of products "covered" by a U.S. process patent.

102. 927 F.2d at 1583-84.

103. "'Dominating' patents are not uncommon." *Phillips*, 865 F.2d at 1253 n.11 (citation omitted).

104. *Cf. Handley, supra* note 5, at 60-61, arguing that a broad initial patent claim could hinder subsequent inventors unsure of the extent to which that broad claim will be

broad protection will encourage patentees to more diligently understand and disclose the nature of their inventions. There are certainly instances in which minor modifications of a biotechnology invention could prove significant and perhaps establish patentability or avoid infringement.¹⁰⁵ In general, however, more expansive protection would prevent competitors from avoiding patent infringement on the basis of compositional changes that did not have a material, structural, or functional impact. Thus, it would secure patent protection from abuse and irrelevance while preventing the theft of significant innovations.

CONCLUSION

As the biotechnology industry expands, there will be other patent infringement disputes similar to *Scripps*, *Genentech*, and *Hormone Research*. Whether biotechnology patent law evolves to the benefit of both the public and competing commercial interests will depend largely on whether the Patent and Trademark Office and the federal courts increase protection by using established chemical patent law as a guide. Hopefully, as the interpretation of biotechnology patent claims becomes common, *Scripps* and *Phillips* will be embraced because they provide rational and much needed direction.

construed to cover their later advancements. However, the granting of broad patent claims did not hinder the development of more mature industries such as automobiles and petrochemicals. See Harold C. Wegner, *Equitable Equivalents: Weighing the Equities to Determine Patent Infringement in Biotechnology and Other Emerging Technologies*, 18 RUTGERS COMPUTER & TECH. L.J. 1, 32 n.111 (1992).

105. The substitution of arginine for methionine in antitrypsin can radically alter protein specificity. STRYER, *supra* note 1, at 255-56.