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PATENTING BIOThERAPEUTICS

Michael A. Sanzo*

I. INTRODUCTION

During the previous decade, the development of methods for producing proteins by recombinant DNA techniques has led to a tremendous growth in the biotechnology industry.¹ There is widespread optimism that the powerful biological tools now available will lead to the development of a host of new drugs for combating disease in humans.² Four recombinant products are presently on the market: insulin, growth hormone, alpha-interferon, and tissue plasminogen activator (hereinafter “tPA”).³ Other drugs are under development and will become available in the near future.⁴ These therapeutic drugs have a number of features in common: all are proteins normally found in the human body; all perform the same functions as therapeutics that they perform naturally; all are presently being manufactured using recombinant DNA methods; and all have been the subject of extensive litigation.⁵ For the purposes of this Article, the group of

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⁴ See OFFICE OF TECHNOLOGY ASSESSMENT, supra note 1, at 161-90; see also THE INTERNATIONAL BIOTECHNOLOGY HANDBOOK, supra note 2.

drugs with these characteristics will be called “biotherapeutics.”

This Article begins with a consideration of the general requirements of patentability under the Patent Act of 1952 (hereinafter the “Act”) and then addresses three issues that have been of particular importance with regard to the patenting of biological inventions.

The first issue raised by biotherapeutics is whether or not these drugs constitute patentable subject matter under section 101 of the Act. The characterization of biological inventions as “products of nature” creates confusion between this issue and that of whether or not a particular product is “novel” and “nonobvious,” as required by sections 102 and 103 of the Act, respectively.

The second issue raised concerns the determination of inventorship. Biological inventions typically result from contributions by many independent researchers, and the criteria for determining who is entitled to patent a particular invention are lacking. It is generally argued that the objective of promoting innovation is best served by adopting a policy of ascribing inventorship to the first party to determine the amino acid sequence of a protein, and by defining the invention in terms of this sequence.

Finally, I address how the “doctrine of equivalents,” as a test for patent infringement, should be applied to biological inventions. The test for infringement under this doctrine is based upon the similarity of molecules with regard to their function. This can lead to

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7. For purposes of this Article, biotherapeutics fall within the statutory definition of what constitutes a drug.
9. Id. §§ 102-03. For examples of cases in which there was an intermingling of the provisions of the patent statute, see In re Fisher, 307 F.2d 948 (C.C.P.A. 1962); Kuehmsted v. Farbenfabriken of Elberfeld Co., 179 F. 701 (7th Cir. 1910); Parke-Davis & Co. v. H.K. Mulford Co., 189 F. 95 (C.C.S.D.N.Y. 1911).
10. The terms “invention” and “inventor” are used in the sense described by Judge Rich: “It is time to settle the point that the terms invent, inventor, inventive, and the like are unrelated to deciding whether the statutory requirements for patentability under the 1952 Act have been met. There is always an invention; the issue is its patentability.” In re Bergy, 596 F.2d 952, 962 (C.C.P.A. 1979). The term “inventorship” refers to the right of a particular party to claim an invention as his. With certain exceptions, it is only this party who may obtain a patent. 35 U.S.C. § 111 (1988).
11. See infra notes 80-94 and accompanying text.
12. See Graver Tank & Mfg. Co. v. Linde Air Prosds. Co., 339 U.S. 605 (1950) (holding that the four flux claims of plaintiff’s patent were infringed by defendant’s device under the doctrine of equivalents).
anomalous results when biological inventions are also defined in
terms of their function.

In discussing the above topics, one particular product, tPA, is
often used as an example. Tissue plasminogen activator is the most
profitable biotherapeutic presently on the market and has been the
source of extensive litigation throughout the past few years.

II. GENERAL REQUIREMENTS OF PATENTABILITY:
NOVELTY AND UTILITY

In order to be patentable, an invention must meet the require-
ments set forth by the Patent Act of 1952. Section 101 of the Act
defines patentable subject matter as "any new and useful process,
machine, manufacture, or composition of matter or any new and
useful improvement thereof." An invention that falls into one of
these categories must then meet the requirements of novelty, utility,
and nonobviousness, as set forth in other provisions of the Act.
Although each of these separate elements must be met for an inven-
tion to be patentable, they have not been equally problematic in

13. Tissue plasminogen activator [hereinafter "tPA"] is a protein used in the treatment of
patients experiencing myocardial infarctions. It acts by binding to and dissolving fibrin clots
obstructing the flow of blood to the heart. It is the most successful drug ever marketed in
terms of gross first-year sales. See Joseph Loscalzo and Eugene Braunwald, Tissue Plasmino-
gen Activator, 319 NEW ENG. J. MED. 925 (1988) (discussing tPA's therapeutic properties);
Barinaga, supra note 3 (discussing tPA's performance as a drug product).

14. See Patents: tPA Variants are Equivalent to Genentech's Patented tPa, 39 PAT.
TRADEMARK & COPYRIGHT J. (BNA) 503 (1990) (discussing a jury's finding that variants of
a genetically engineered protein (tPA) infringe patents of Genentech, Inc., under the doctrine
of equivalents); Paul G. Cole, United Kingdom: Revocation of Genentech's British Patent for
T-PA is Sustained by Court of Appeal, 37 PAT. TRADEMARK & COPYRIGHT J. (BNA) 206
(1988) (discussing the revocation of Genentech's patent for tPA in the United Kingdom); see
also David Swinbanks, Problems Over TPA Patent for Genentech in Japan, 333 NATURE 587
(1988); Carol Ezzell, Initial Sales of Genentech's TPA Set New Records, 331 NATURE 202
(1988) (reporting that, during the first six weeks that tPA was available, it accumulated $58
million in sales); M. Mitchell Waldrop, Companies Vie Over New Heart Drug, 237 SCIENCE
120 (1987) (discussing Genentech's battle to maintain its patent for tPA in the United King-
dom).

15. See supra note 10 for a definition of "invention."

16. See generally 35 U.S.C. §§ 1-376 (1988) (setting forth the requirements to obtain a
patent).

17. Id. § 101.

18. Id. §§ 102, 103, 112.

19. See Diamond v. Diehr, 450 U.S. 175 (1981) (holding that the patent was not invalid
for lack of novelty); General Motors Corp. v. Toyota Motor Co., 667 F.2d 504 (6th Cir.
1981) (holding that the patent was not invalid for obviousness); American Seating Co. v. Na-
tional Seating Co., 586 F.2d 611 (6th Cir. 1978) (holding that the patent was invalid because
the context of biological inventions. Neither questions of novelty nor questions of utility have been the usual subjects of dispute in patents on biotherapeutics.

The requirement of novelty is fulfilled as long as there is no single description in the prior art that contains all of the elements of the invention. Even trivial differences between the invention and the prior art will be sufficient to make the invention "novel." Not surprisingly, inventors have little trouble in meeting this standard.

Similarly, the utility requirement seldom presents a problem for inventors. An invention is not required to be superior to other similar inventions. It is sufficient that it has some beneficial use. This idea was expressed by Justice Story more than 150 years ago:

It is not necessary to establish, that the invention is of such general utility, as to supersede all other inventions now in practice to accomplish the same purpose. It is sufficient, that it has no obnoxious or mischievous tendency, that it may be applied to practical uses, and that so far as it is applied, it is salutary.

The cost of litigation alone makes it unlikely that a patent dispute will arise over a product's inability to meet such minimal requirements. It is also unlikely that corporations will invest the capital needed to develop a biotherapeutic without first obtaining substantial evidence that it will be of considerable value as a product.

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20. See Kalman v. Kimberly-Clark Corp., 713 F.2d 760 (Fed. Cir. 1983) (holding, inter alia, that the patent was valid because it satisfied the requirements of novelty, utility and nonobviousness).

21. See, e.g., Eibel Process Co. v. Minnesota & Ont. Paper Co., 261 U.S. 45 (1923) (holding, inter alia, that an increase of at least 20% in the daily output of paper product was sufficiently weighty evidence to sustain the presumption of new and useful).

22. National Slug Rejecters, Inc. v. A.B.T. Mfg. Corp., 164 F.2d 333 (7th Cir. 1947); see also In re Oberweger, 115 F.2d 826 (C.C.P.A. 1940) (holding that a small degree of utility is sufficient to support a patent); Fuller v. Berger, 120 F. 274 (7th Cir. 1903) (holding that an invention is not void for lack of utility because it was used for immoral purposes).


25. On average, it costs more than $125 million to develop a new drug and to obtain
In contrast to novelty and utility, questions concerning inventorship, nonobviousness, and whether or not an invention constitutes patentable subject matter occur repeatedly. These questions are considered below.

III. DO BIOThERAPEUTICS CONSTITUTE PATENTABLE SUBJECT MATTER? BIOThERAPEUTICS AS “PRODUCTS OF NATURE”

Determining what constitutes patentable subject matter under section 101 of the Act has proven to be one of the most difficult and controversial tasks in patent law. The problem is compounded by the fact that courts often fail to draw a distinction between the question of what constitutes patentable subject matter and the question of whether or not that subject matter meets the other requirements of patentability. The problem is exemplified by Judge Rich’s comments concerning the Supreme Court’s decision in Parker v. Flook:27

[W]e find in Flook an unfortunate and apparently unconscious, though clear, commingling of distinct statutory provisions which are conceptually unrelated, namely, those pertaining to the categories of inventions in § 101 [of the Act] which may be patentable and to the conditions for patentability demanded by the statute for inventions within the statutory categories, particularly the nonobviousness condition of § 103 . . . .

. . . . Thus, the questions of whether a particular invention is novel or useful are questions wholly apart from whether the invention falls into a category of statutory subject matter.28

The commingling, by courts, of unrelated provisions of the patent statute is typically manifested by the denial of patents for biological inventions because they are “products of nature.”29 There is, FDA approval for sale. Allen E. Cato, The Challenge of the Clinical Development of Drugs, in CLINICAL DRUG TRIALS AND TRIBULATIONS 1, 3-5 (Allen E. Cato ed., 1988). 26. In re Walter, 618 F.2d 758 (C.C.P.A. 1980). Judge Rich, writing for the court, was of the opinion that the “determination of statutory subject matter under § 101 [of the Act] in the field here involved has proved to be one of the most difficult and controversial issues in patent law.” Id. at 764. 27. 437 U.S. 584 (1978). 28. In re Bergy, 596 F.2d 952, 959, 960-61 (C.C.P.A. 1979); see also In re Sarkar, 588 F.2d 1330 (C.C.P.A. 1978) (holding, inter alia, that questions of novelty and nonobviousness are irrelevant considerations to section 101 determinations). 29. See, e.g., Diamond v. Chakrabarty, 447 U.S. 303 (1980) (holding that plaintiff’s live, human-made micro-organism was patentable because the new bacteria had different characteristics from any found in nature, and that the fact that it was alive was without legal signifi-
in fact, nothing in the patent statute precluding the patenting of products of nature. To the extent that such statements have a statutory basis, they are really contentions that inventions are unpatentable either because they lack novelty or are obvious.\(^{30}\)

A. "Product of Nature" as a Contention that an Invention Lacks Novelty

With regard to novelty, a "product of nature" denial is a contention that, because the product occurs naturally, it is not "new," as is required under section 101 of the Act.\(^{31}\) Under this interpretation, the word "new" means never having existed before. However, such an interpretation has no justification. Congress explicitly stated that the meaning of "new," as used in section 101, is defined by section 102 of the Act. "Section 101 sets forth the subject matter that can be patented, 'subject to the conditions and requirements of this title.' The conditions under which a patent may be obtained follow, and section 102 covers the conditions relating to novelty."\(^{32}\) "[The] statute is split into two sections, section 101 relating to the subject matter for which patents may be obtained, and section 102 defining statutory novelty."\(^{33}\)

When restated as a question of novelty under section 102, courts have had little difficulty finding that biological inventions are patentable. For example, in considering whether a prostaglandin that had been purified from sheep prostate glands fulfilled the statutory requirement of novelty, the court in *In re Bergstrom*\(^{34}\) held:

> It seems to us that the answer to that question [whether or not the purified prostaglandin was novel] is self-evident: by definition, pure materials necessarily differ from less pure or impure materials and,

\(^{30}\) See Comment, The Patentability of Living Organisms Under 35 U.S.C. § 101: *In re Bergey*, 91 Harv. L. Rev. 1357, 1360 (1978) (arguing that courts that have considered the patentability of products of nature have rejected the patent claim on statutory requirements like novelty or obviousness).

\(^{31}\) *Id.* at 1358.

\(^{32}\) H.R. REP. No. 1923, 82d Cong., 2d Sess. 6 (1952).


\(^{34}\) 427 F.2d 1394 (C.C.P.A. 1970).
if the latter are the only ones existing . . . the "pure" materials are "new" with respect to them.\textsuperscript{35}

\section*{B. "Product of Nature" as a Contention that an Invention Was Obvious}

The second potentially valid contention that may be expressed as a denial based on an invention being a "product of nature" is that the invention was obvious.\textsuperscript{36} The analysis is greatly simplified once it is recognized that what is at issue is not whether or not an invention falls within the section 101 categories of patentable subject matter, but, rather, whether or not it fulfills the requirement of nonobviousness of section 103 of the Act. Under section 103,

[a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title [even if the requirement of novelty is met], if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.\textsuperscript{37}

Section 103 was first interpreted by the Supreme Court in \textit{Graham v. John Deere, Co.}\textsuperscript{38} The Court stated that "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent."\textsuperscript{39} With regard to biotherapeutics, courts have found that sufficient differences exist where the invention offers some clear therapeutic advantage over previous forms of the product. For example, in considering the patentability of vitamin B-12, a natural product of the liver, a federal district court wrote:

Before [the inventors] made it available to the world, pure crystalline vitamin B-12, as described and claimed in the '794 patent, did not exist . . . . The new product had such advantages over the

\begin{footnotesize}
\footnotetext{35}{\textit{Id.} at 1401-02 (footnote omitted).}
\footnotetext{36}{See \textit{Comment}, \textit{supra} note 30, at 1358.}
\footnotetext{37}{35 U.S.C. § 103 (1983).}
\footnotetext{38}{383 U.S. 1 (1966).}
\footnotetext{39}{\textit{Id.} at 14 (quoting S. REP. No. 1979, 82d Cong., 2d Sess. 6 (1952); H.R. REP. No. 1923, 82d Cong., 2d Sess. 7 (1952)).}
\end{footnotesize}
earlier liver extracts that it not only replaced them, but became, and remains to this day, the universal treatment for pernicious anemia. The new product has completely eliminated the harmful side effects of the old liver preparations.40

It is important to recognize that it was not merely the change in form (i.e., the purification) that made the vitamin patentable, but, rather, that the change led to a product with substantially improved properties.

IV. DEFINING INVENTIONS BY STRUCTURE: THE PROBLEM OF DETERMINING INVENTORSHIP

A. Phases in the Development of Biotherapeutics

Given that biotherapeutics are patentable subject matter, what basis should be used for determining inventorship? These products are typically developed by many different research groups performing similar kinds of experiments.41 The problem, then, is determining


41. There are a number of articles that summarize the development and therapeutic uses of the most promising biotherapeutics. Included among these are the following: Jerome E. Groopman et al., Hematopoietic Growth Factors, 321 NEW ENG. J. MED. 1449 (1989) (discussing the important applications of hematopoietic growth factors); Charles H. Kirkpatrick, Biological Response Modifiers—Interferons, Interleukins, and Transfer Factor, 62 ANNALS ALLERGY 170 (1989) (reviewing the effects of certain cell-derived soluble factors on the immune system); O. Mehls & R.N. Fine, The Use of Recombinant Growth Hormone for Treatment of Growth Failure in Uremia, 9 SEMINARS NEPHROLOGY 43 (1989) (providing a perspective for the therapeutic use of human recombinant growth hormones); Glenn F. Pierce et al., The Use of Purified Clotting Factor Concentrates in Hemophilia, 261 JAMA 3434 (1989) (discussing the effects of purified clotting factors on eliminating greater amounts of infectious agents in hemophiliacs); Claudio Ponticelli & Stefano Casati, Correction of Anemia with Recombinant Human Erythropoietin, 52 NEPHRON 201 (1989) (concluding that anemia can be fully corrected by recombinant human erythropoietin); H. Thomas & K. Sikora, Biological Approaches to Cancer Therapy, 17 J. INT’L MED. RES. 191 (1989) (stating that the potential permutations and applications of biological therapy for cancer are great); C.G.D. Brook, Treatment of Growth Deficiency, 30 CLINICAL ENDOCRINOLOGY 197 (1988) (discussing the causes of growth deficiency and the effect of biosynthetic growth hormones on the deficiency); Robert Califf et al., Experience with the Use of tPA in the Treatment of Acute Myocardial Infarction, 17 ANNALS EMERGENCY MED. 1176 (1988) (arguing that thrombolytic therapy offers the potential to reduce substantially the mortality of patients with acute myocardial infarction when given medical attention in the early stages); Robert A. Figlin, Biotherapy with Interferon-1988, 15 SEMINARS ONCOLOGY 3 (1988) (reviewing the effects of interferon therapy on human malignancy treatments); Leopold Flohé, Superoxide Dismutase for
which of many possible inventors should be entitled to claim that she
made the invention. The developmental process may be divided into
four distinct phases: initial observations, determination of structure,
large scale production, and clinical testing and commercial production.

Phase I: Initial Observations: Typically, suspicions concerning
the existence of a novel biological factor begin with observations
made on impure extracts prepared from tissues or cells. For example,
the first indication of the existence of tPA came in 1947 when Tage
Astrup observed that certain crude tissue extracts dissolved fibrin.\(^{42}\)
Since the activity did not appear to be due to any of the factors that
were then known to have fibrinolytic activity, Astrup speculated that
there might be a unique factor causing the effect.\(^{43}\) At the time, it
was not clear that the observation had any therapeutic significance or
that a new factor existed. During the following years, Astrup and
other investigators continued to make observations on impure mix-
tures.\(^{44}\) Although the results were not entirely consistent with one
another, taken together they presented strong evidence for the exis-
tence of a new fibrin-dissolving protein.

Phase II: Determination of Structure: Once there is evidence of
the existence of a new factor of potential therapeutic value, develop-
ment may follow one of two different paths. In some instances, re-
searchers purify the protein to homogeneity,\(^{45}\) determine its full or

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Therapeutic Use: Clinical Experience, Dead Ends and Hopes, 84 MOLECULAR & CELLULAR
BIOCHEMISTRY 123 (1988) (reviewing the achievements and drawbacks of superoxide
dismutase); Jordan Gutterman, Overview of Advances in the Use of Biological Proteins in
Human Cancer, 15 SEMINARS ONCOLOGY 2 (1988) (arguing that major advances in the use
of biologics should significantly contribute to improving the survival of cancer patients); Craig
M. Kessler et al., Acute Pulmonary Embolism Treated with Thrombolytic Agents: Current
Status of tPA and Future Implications for Emergency Medicine, 17 ANNALS EMERGENCY
MED. 1216 (1988) (concluding that innovative approaches to the use of thrombolytic agents
may maximize their effectiveness).

42. Tage Astrup & Per M. Permin, Fibrinolysis in the Animal Organism, 159 NATURE
681 (1947) (reporting that profibrinolysin can be transformed into fibrinolysin by an activator
found in animal tissue cells).

43. Id. at 682; see also Tage Astrup, Fibrinolysis in the Organism, 11 J. HEMATOLOGY
781 (1956) (providing an analytical review of the fibrinolytic process).

44. See Sten Mullertz, A Plasminogen Activator in Spontaneously Active Human Blood,
82 PROC. SOC'Y EXPERIMENTAL BIOLOGY & MED. 291 (1952) (reviewing an experiment on
fibrinolytic activity); see also Astrup, supra note 43.

45. There is no absolute way of showing that a protein is pure. The best that can be
done is to show that separation methods fail to reveal any inhomogeneities in a preparation;
hence, the term "purification to homogeneity." See ABRAHAM WHITE ET AL., PRINCIPLES OF
partial amino acid sequence, and use this information to clone the corresponding gene. In other instances, researchers rely on the immunological or biological properties of a protein in order to clone its gene directly. The full amino acid sequence of the protein may then be deduced by sequencing nucleic acid.

Sequence determination represents a central event in the development of a biotherapeutic. For the first time, a specific biological function may be associated with a well defined biochemical structure. The time period from the initial observations suggesting the existence of a molecule to the time its structure is determined can be extensive. For example, the sequence of tPA was not determined until over thirty years after the initial observation by Astrup.

Phase III: Large Scale Production: During the first two phases of development, the structure and function of a potential biotherapeutic are determined. This information is sufficient to form the basis of a patent. A separate question is whether or not the invention will be of any practical therapeutic value. In order to determine this, sufficient quantities of the protein must be produced to evaluate its clinical properties—first in animals and later in humans. The importance of being able to scale up production should not be underestimated; it has been a major stumbling block in the development of even the most promising of drugs.


47. See, e.g., J. Michael Bishop, Oncogenes, Sci. Am., Mar. 1982, at 81 (discussing the study of oncogenes, which make up tumor viruses, and which are believed to cause cancerous growth in healthy cells); see also Henry A. Erlich et al., Immunological Detection and Characterization of Products Translated from Cloned DNA Fragments, in 68 Methods in Enzymology 443 (Ray Wu ed., 1979) (discussing the use of cloned DNA to detect functions and immunological properties of proteins).


50. The FDA requirements that must be met for a new drug to be approved may be found in 21 U.S.C. section 355. Regulations cover animal testing, 21 C.F.R. §§ 312.22(c), 312.23 & 312.1(a)(2) (1990), as well as three separate phases of clinical trials. 21 C.F.R. § 312.21(a)-(c) (1990). Upon completion of clinical trials, a drug sponsor may submit a new drug application ("NDA") according to the procedures set forth in 21 C.F.R. section 314.50 (1990).

51. See, e.g., Sidney Pestka, The Purification and Manufacture of Human Interferons, Sci. Am., Aug. 1983, at 37-38 (discussing the fact that the shortage and high cost of inter-
Phase IV: Clinical Testing and Commercial Production: If, based upon research in animals, it appears that a drug is a promising candidate for commercialization, it will be evaluated in humans and a determination will be made as to whether or not it can be profitably manufactured. Clinical evaluation is an expensive undertaking that typically requires years to complete.

An examination of the progression described above suggests that inventorship will be determined by events that occur during either Phase I or Phase II. Although patents may be awarded on inventions made during either of these phases, it is likely that only Phase II patents will be of any long-term value. Moreover, as discussed below, there are logical and practical reasons for adopting a policy of determining inventorship based solely upon events occurring during Phase II.

B. Phase I Patents

During the initial phase of development, observations are made on cell or tissue extracts and on partially purified preparations. Although patents may potentially be awarded on such materials, there are a number of reasons why such patents are likely to be of minimal value. First, patents on impure preparations lack specificity. The biological activities observed in such preparations may be due to the interaction of several proteins, or to factors that are not proteins at all. Uncertainties concerning the nature of factors are compounded by uncertainties caused by the complex biological assays that are typically used to make observations. Consequently, it is difficult to show that an alleged infringer used the same factor as that described

feron, a protein released by cells exposed to a virus, which then enables other cells to resist the virus, has limited cancer studies and studies of the protein’s effectiveness against viruses).

52. See 21 C.F.R. § 312.21 (a)-(c) (1990).

53. The average time required to complete the clinical development of a new drug and obtain FDA approval is approximately nine years. The average remaining patent life of a drug after approval for sale is approximately seven years. See Cato, supra note 25, at 5-6.

54. See In re Bergstrom, 427 F.2d 1394 (C.C.P.A. 1970) (holding that the distinction between "pure" materials and less pure or "impure" materials results in the potential patentability of either, or possibly both, materials); see also In re Williams, 171 F.2d 319 (C.C.P.A. 1948) (holding that, where a patent already exists for an impure compound, a patent claim for a pure ingredient of this compound may fail for lack of invention, although not for lack of novelty).

55. See Fedor Bachmann et al., Partial Purification and Properties of the Plasminogen Activator from Pig Heart, 3 BIOCHEMISTRY 1578 (1964) (illustrating the uncertainties created by the use of impure preparations).

56. Id.
in a patent.

A second reason why Phase I patents are likely to be of limited value is that the inventions themselves are at a competitive disadvantage. Although crude preparations have occasionally been used to treat patients in the past, proteins made by recombinant methods and then purified prior to clinical administration offer such substantial technical and therapeutic advantages that it is unlikely that extracts containing undefined factors will be used to an appreciable extent in the future.

Finally, patents on partially purified tissue extracts could be easily circumvented by competitors. Such patents would apply only to the specific preparation described and not to the factor within the preparation responsible for the observed activity. Thus, a new and patentable invention could be obtained by simply altering the extraction or purification procedure.

C. Phase II Patents

Under section 112 of the Act, an invention must be specifically and accurately defined. In order to define specifically a biotherapeutic, a researcher must carry out two closely related processes. First, she must develop a procedure for obtaining the biologically active protein (or its gene) in pure form and, second, she must determine its amino acid sequence. Whereas different proteins may


58. One major disadvantage associated with the use of cell or tissue extracts is that, if the source material is of human origin, there is likely to be a severe limitation on the amount of such material available. See, e.g., Lawn & Vehar, supra note 46; see also Pestka, supra note 51. In contrast, cloned genes produce an essentially unlimited amount of source material. Id.

Another major disadvantage is that tissue extracts may be contaminated with pathogens that are harmful or deadly to the recipients of such extracts. This danger is eliminated when the proteins are produced by recombinant means. See infra note 64 and accompanying text; see also Genetic Engineering May Cut Risk of Blood Infection in Hemophiliacs, N.Y. TIMES, Dec. 27, 1990, at A16 (reporting that many hemophiliacs became infected with the AIDS virus after receiving a blood-clotting protein derived from tainted blood, but that such infection could be avoided by using a recombinant protein that is now being tested).

59. See Bergstrom, 427 F.2d 1394.


61. The purification procedure is analogous to a map describing how to get to a specific place. The amino acid sequence is analogous to an address that exactly defines that place and distinguishes it from all others.
have similar biological functions, their amino acid sequences are absolutely unique.\(^6\) Since it is not until a researcher determines this sequence that a biotherapeutic has been unambiguously identified, it follows logically that the first researcher to make such a determination should be entitled to inventorship.\(^6\)

Determining inventorship based upon priority in defining the amino acid sequence of a protein makes sense for other reasons as well. Purification and sequence determination are key events in the evaluation of the therapeutic potential of a protein. Until it has been identified and is available in pure form, there is no way to determine whether an observed therapeutic effect is due to a protein or to some impurity present in the administered preparation.

Moreover, in light of recent experiences in which patients treated with impure biological materials have developed AIDS or Creutzfeldt-Jakob disease, it is unlikely that crude drug preparations will be considered to be suitable for clinical use in the future.\(^6\) The transformation of a biological compound from a state of therapeutic unsuitability to a state at which therapeutic applications become feasible has traditionally provided grounds for patentability.\(^6\) For example, in consid-

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6. For example, tPA, pro-urokinase, and streptokinase all have similar functions, but they differ greatly in structure. See H. Straub et al., Thrombolytic Effect of Streptokinase on Coronary Artery Occlusion in Acute Myocardial Infarction by Conventional Intravenous Administration Over 24 Hours, in 7 PROGRESS IN FIBRINOLYSIS 39-40 (John F. Davidson et al., eds. 1985) (illustrating the functions and properties of streptokinase); see also D. Collen & H.R. Lijnen, Thrombolysis with Human Tissue-Type Plasminogen Activator, in 7 PROGRESS IN FIBRINOLYSIS, supra, at 66-70 (illustrating the functions and properties of tPA); V. Gurewich et al., Fibrin-Specific Lysis of Pulmonary Emboli by Pro-Urokinase (Pro-UK) in Rabbits and Dogs, in 7 PROGRESS IN FIBRINOLYSIS, supra, at 59-62 (illustrating the functions of pro-urokinase).

63. While an impure preparation may be defined in terms of the process used to make it, the factor within the preparation responsible for the observed biological activity is unknown and unpatentable, per se. See Merck & Co. v. Olin Mathieson Chem. Corp., 253 F.2d 156 (4th Cir. 1958); see also In re Merz, 97 F.2d 599 (C.C.P.A. 1938); Kuehmsted v. Farbenfabriken of Elberfeld Co., 179 F. 701 (7th Cir. 1910).


65. See Merck & Co., 253 F.2d 156; Sterling Drug Inc. v. Watson, 135 F. Supp. 173 (D.D.C. 1955) (holding that a patent application that disclosed sufficient "unexpected and unobvious beneficial properties" not possessed by similar compounds or prior art to show patentability may be approved even though the compound could be found in its natural form in the human body); Smith, Kline & French Lab. v. Clark & Clark, 62 F. Supp. 971 (D.N.J. 1945), modified, 157 F.2d 725 (3d Cir. 1946); Parke-Davis & Co. v. H.K. Mulford Co., 189
erating the patentability of aspirin, the Court of Appeals for the Seventh Circuit held:

[I]t makes no difference, so far as patentability is concerned, that the medicine thus produced is lifted out of a mass that contained, chemically, the compound; for, though the difference between [the two] be one of purification only—strictly marking the line, however, where the one is therapeutically available and the others were therapeutically unavailable—patentability would follow.66

Judge Learned Hand set forth essentially the same principle in a case concerning the patentability of purified adrenalin:

But, even if [adrenalin] were merely an extracted product without change, there is no rule that such products are not patentable. Takamine was the first to make it available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.67

Finally, determining inventorship based on priority in defining the amino acid sequence of a biotherapeutic provides a simple, straightforward test. Much of the patent litigation associated with biological compounds stems from the fact that the criteria presently being used by courts is not at all clear.

D. Tissue Plasminogen Activator Patents: The Problem of Functional Definitions

Many of the problems created by defining biological inventions in terms of function rather than structure are exemplified by the patents on tPA owned by Genentech.68 Patent No. 4,752,603 (hereinafter "603") is based upon experiments in which tPA was purified from the conditioned medium of Bowes melanoma cells, and it defines tPA solely on the basis of its functional attributes.69 Specifically, the in-

F. 95 (C.C.S.D.N.Y. 1911), rev'd on other grounds, 196 F. 496 (C.C.A.N.Y. 1912) (holding that a substance extracted from animal tissue for medicinal use, which is practically and therapeutically new, may be patentable even though it differs from earlier preparations only in its degree of purity).
66. Kuehmsted, 179 F. at 705.
67. Parke-Davis, 189 F. at 103.
68. See R. Stephen Crespi, Claims on Tissue Plasminogen Activator, 337 Nature 317 (1989) (summarizing the claims made in these patents).
69. See Dingemen C. Rijken & Désiré Collen, Purification and Characterization of the
ventors claim a "[h]uman 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 tPA as [reference standard] . . . ." It is difficult to see what criteria would justify the broad protection afforded by these claims. The existence of a human plasminogen activator distinct from urokinase was known long before the work described in the patent and the specific activity cited appears to have been incorrect by a wide margin.

Patent No. 4,766,075 (hereinafter "075") claims the sequence for the human tPA gene. In contrast to the claims set forth in the 603 patent, this serves to distinguish clearly the protein being claimed from the prior art, represents a definite scientific advance, and is clearly deserving of patent protection. Unfortunately, the 075 patent does not confine itself to structural definitions. The patent, in effect, precludes competitors from using any recombinant techniques for expressing or modifying the tPA gene. Again, it is difficult to understand the criteria that would justify the granting of such protection. The methods that were used by the inventors in cloning and expressing tPA were not novel, and it is unusual to award process patents for old methodology simply because it is being applied to a new problem.

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70. United States Patent No. 4,752,603, col. 10, ll. 36-44 (June 21, 1988).
71. See Genentech, Inc. v. Wellcome Found., 14 U.S.P.Q. 2d (BNA) 1363, 1365 (D. Del. 1990); see also Crespi, supra note 68, at 317.
72. "Specific activity" is expressed as the amount of enzymatic activity that a particular preparation has per amount of protein. As protein preparations become increasingly pure, their specific activities should increase. ALBERT L. LEININGER, BIOCHEMISTRY 208-09 (2d ed. 1975). The abbreviation "IU/mg." is defined in the 603 patent as standing for international units per milligram.
73. See Genentech, Inc., 14 U.S.P.Q. 2d at 1369.
75. Id. at col. 5, ll. 21-34. The patent states:
The potential exists, in the use of recombinant DNA technology, for the preparation of various human tissue plasminogen activator derivatives, variously modified by resultant single or multiple amino acid substitutions, deletions, additions or replacements, for example, by means of site directed mutagenesis of the underlying DNA . . . . All such allelic variations and modifications resulting in derivatives of human tissue plasminogen activator are included within the scope of this invention . . . .

Id.
76. See Crespi, supra note 68, at 318.
77. See Amgen, Inc. v. United States Int'l Trade Comm'n, 902 F.2d 1532, 1534 (Fed. Cir. 1590) (examiner of the Patent and Trademark Office rejecting claims to the process of
A policy of limiting patent claims to the specific structure identified by an inventor would avoid the kind of overinclusive functional descriptions encountered in the Genentech patents. It is important to recognize, however, that, even though a researcher who had isolated a protein with a unique amino acid sequence would be entitled to be the inventor of that molecule, this does not necessarily mean that he would be awarded a patent. He must show that the protein he has obtained does not infringe upon similar proteins discovered by others. It is in this regard, and not with regard to inventorship, that the functional properties of a molecule are of major importance.

V. FUNCTIONAL CHARACTERISTICS OF BIOThERAPEUTICS AND PATENT INFRINGEMENT

A. Functional Properties as a Test for Infringement

While the structure of biological inventions is of prime importance in questions of inventorship, the therapeutic properties of these molecules are of prime importance in questions of infringement. If all that was necessary to avoid a claim of infringement was to show that the challenged protein differed structurally from the patented protein, patents on biotherapeutics would be of little or no value. They could be avoided by simply introducing a trivial change in the amino acid sequence of the protein or by isolating a naturally occurring variant.

A balance between the overly broad protection of patents based on function and the overly narrow protection of patents based strictly on structure can be achieved by adopting the following policy: al-
though a structurally altered form of a biotherapeutic is novel within the meaning of section 102 of the Patent Act, it is not sufficiently new to escape a charge of infringement unless the structural differences are nontrivial with respect to the therapeutic properties of the molecule.

Such a position is consistent with past judicial policy. In *Ziegler v. Phillips Petroleum Co.*,81 the court stated that, "[i]n recognition of the fact that a patent would be virtually worthless if it did not protect against devices which incorporate unimportant variations of the patented device, courts [have] developed the doctrine of equivalents . . ."82 Under this doctrine, two inventions that do the same work in substantially the same way to achieve substantially the same result are the same.83 It is important to note that this is a functional test, based on what the invention does. As such, it can lead to problems when applied to biological inventions that have also been defined in functional terms.84 This can best be seen using a concrete example and, once again, tPA provides an illustration of the kind of problem that can arise.

**B. Patents on tPA: Problems in Applying the Doctrine of Equivalents to Inventions Defined by Their Functions**

One of the main difficulties associated with the use of tPA as a therapeutic is that it is rapidly cleared from the plasma (half-life = three to six minutes).85 As a result, large quantities of the drug must be continually infused in order to attain therapeutically effective blood concentrations.86 Burroughs Wellcome modified the structure of tPA in such a way that the plasma half-life of the molecule was increased to about sixty minutes.87

All other things being equal, it is difficult to imagine a change with greater therapeutic implications. The amount of damage caused

81. 483 F.2d 858 (5th Cir. 1973).
82. Id. at 868.
84. For a discussion of the problems created by functional definitions with regard to inventorship, see supra notes 68-79 and accompanying text. The present section deals with the problem of functional definitions with regard to infringement.
85. See Loscalzo & Braunwald, supra note 13.
by a heart attack is directly related to the length of time that the heart is deprived of oxygen due to an occluded blood vessel. Since tPA must be infused, a heart attack victim cannot ordinarily receive treatment before arriving at a hospital. Increasing the half-life of the molecule opens up the possibility of administering tPA as a single bolus injection. Thus, it might be possible for an individual at high risk of suffering a heart attack to carry tPA for self-administration. Also, since substantially less tPA would be required to achieve the same plasma concentration, it should be possible to reduce the cost of treatment (presently about $2,000).89

In spite of these advantages, a jury in the District Court for the District of Delaware found that Wellcome’s version of tPA infringed upon Genentech’s patents.90 This decision appears to be a clear misapplication of the doctrine of equivalents and to be inconsistent with the patent statute’s objective of promoting innovation.

The jury’s decision becomes more understandable, however, when one considers Wellcome’s invention in light of Genentech’s patent claims. As stated previously, these encompass all human plasminogen activators, immunologically distinct from tPA and with a specific activity of about 500,000 IU/mg.91 Wellcome’s version of the tPA molecule had all of these characteristics. Since the claims made on inventions that have been awarded patents by the Patent and Trademark Office are given a presumption of validity,92 a jury might be persuaded that infringement had occurred regardless of the potential therapeutic advantages of Wellcome’s form of the molecule. In this regard, it is worth noting that, overall, the similarities in the tPAs

88. See M. Verstraete, Even if the Efficacy of Intracoronary Thrombolysis is Proven, This Approach is a Death Issue in Terms of Public Health, in 7 PROGRESS IN FIBRINOLYSIS, supra note 62, at 25-29 (stating that the timely reopening of an acutely occluded coronary artery actually saves more myocardial tissue; therefore, improving myocardial function, reducing the reinfarction rate, and decreasing early and late mortality are reasonable assumptions); W.H. Bleifeld et al., The Clinical Relevance of Opening a Coronary Artery in Patients with Acute Myocardial Infarction, in 7 PROGRESS IN FIBRINOLYSIS, supra note 62, at 30-38 (discussing the analysis of the underlying mechanisms leading to an acute myocardial infarction, methods used for reperfusion, results of thrombolytic treatment, especially with regard to rate of reopening ventricular function and post-thrombolytic treatment).

89. Marcia Barinaga, Genentech’s Boom is Boosted by New Clinical Trial Data, 332 NATURE 387 (1988).


91. See supra notes 70-73 and accompanying text.

far outweigh their differences: both lead to the reperfusion of occluded blood vessels by promoting the dissolution of fibrin clots; both work by converting plasminogen to plasmin; and the vast majority of the amino acids in the molecules are identical. Using the most typical phrasing of the doctrine of equivalents test, it might be concluded that the molecules performed substantially the same work, in substantially the same way, to achieve substantially the same result.

The jury was, therefore, presented with a molecule that was clearly different from Genentech's both structurally and in terms of a therapeutically significant property, but that nevertheless fell within the literal scope of Genentech's claims. This conflict is the direct result of the Patent Office permitting per se patents on biotherapeutics such as tPA to be based strictly on a functional description of the molecule. Since an inventor cannot describe all of the properties that may have a significant impact on therapeutic potential, patents based on biological functions give patent holders an undeservedly broad range of equivalents. As a consequence, new inventions that offer substantial advantages over patented molecules may nevertheless be found to infringe.

Requiring that patents describe biological inventions in terms of structure would avoid these problems and would greatly simplify disputes over infringement. One of the main advantages of such a requirement would be that it would allow the scope of patent claims to be determined by the molecules themselves. Side by side comparisons could be made between the patented and the allegedly infringing molecules with respect to any function, even those whose therapeutic significance was not appreciated at the time the patent application was filed.

VII. CONCLUSION

Patents are limited monopolies granted for the purpose of promoting innovation. To succeed, they must strike a balance between protecting inventions and preserving competition. If patent claims are permitted to exceed the scope of an inventor's contribution, then competition is unfairly eliminated and innovation is repressed. As the

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93. See Graver Tank & Mfg. v. Linde Air Prods., 339 U.S. 605, 608-09 (1950) (providing 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.").

94. See supra notes 83, 93 and accompanying text.
patent dispute between Burroughs Wellcome and Genentech demonstrates, this is exactly the effect of allowing biotherapeutics to be defined based upon their functional properties. Since a molecule has an unlimited number of potentially important functions, patents in which inventions are defined in this way must necessarily be ambiguous. Questions of novelty and infringement may become confused and difficult to resolve.

A policy that requires biological inventions to be defined in structural terms would avoid the patent problems created by the inherent ambiguities of functional definitions. Under such a policy, a biotherapeutic with a structure that had not been previously described would be novel and the party who determined that structure would be entitled to inventorship. Competition among inventors would be preserved by limiting patent claims to the exact structure described and by using the functional characteristics of proteins to settle questions of infringement. For example, if A patented a protein and later, B claimed a protein that differed in only three amino acids, then the question of whether B’s invention infringed upon A’s would depend upon whether those particular amino acids were important for some significant function. Thus, inventors would be encouraged to look for natural variants with better therapeutic properties and to attempt to improve the therapeutic properties of proteins through techniques such as site-directed mutagenesis.

Finally, regardless of the policy adopted, patent disputes over biological molecules will be simplified by keeping clearly in mind the exact provisions of the patent statute that are at issue. The commingling of distinct statutory sections and the misleading characterization of biological inventions as “products of nature” has created considerable confusion. These practices serve only to obscure issues and to make court battles over the patent rights to biological inventions more probable and less predictable.