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BIOTECHNOLOGY PATENT LAW: PERSPECTIVE OF THE FIRST SEVENTEEN YEARS, PROSPECTIVE ON THE NEXT SEVENTEEN YEARS

LORANCE L. GREENLEE*

I. INTRODUCTION

The era of biotechnology began in 1973 when Stanley N. Cohen and Herbert W. Boyer reported that a gene could be cut from the DNA of one organism, recombined *in vitro* with DNA of a host organism, and re-introduced into cells of the host to confer the gene's characteristic trait to the host.[1] The industry which sprang up to exploit the potential of Cohen and Boyer's recombinant DNA technology has now existed for seventeen years—the lifetime of a United States patent.[2] In the world of patent practice this year constitutes a divide, a point when it is appropriate to take stock of the legal developments of the preceding patent lifetime and to consider what may be in store for practitioners in the next seventeen years.

This article is divided into two sections. The first provides an historical perspective of the first seventeen years of biotechnology patent law. The second section examines some current trends and how they may affect the development of the law over the next seventeen years.

II. HISTORICAL PERSPECTIVE

A. *Public Apprehension*

Biotechnology grew up under a floodlight of intense public scrutiny and debate. Many of the new companies formed to exploit the commercial potential of the scientific advances of the preceding two decades generated publicity to aid in attracting investors. Scientists publicly debated their concerns about the possible hazards or disastrous consequences of certain types of experiments. Some feared the possible creation of new pathogens which, if improperly contained, could spread into the environment.

In response to the concerns, the National Institutes of Health promulgated guidelines for conducting recombinant DNA research.

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1. *See* Cohen & Boyer, *Construction of Biologically Functional Bacterial Plasmids in Vitro*, 70 PROC. NAT'L ACAD. SCI. 3240 (1973)[hereinafter Cohen & Boyer]. The following United States patents have issued to Cohen and Boyer on their "biologically functional molecular chimeras": U.S. Patent No. 4,237,224, issued December 2, 1980; U.S. Patent No. 4,468,464, issued August 28, 1984; and U.S. Patent No. 4,740,470, issued April 26, 1988.

2. 35 U.S.C. § 154 (1988)(patent term is seventeen years).

Subsequently, these guidelines underwent a series of revisions that resulted in an increased number and scope of allowable activities. The revisions were a result of improved understanding of the actual risks involved from working with genetically engineered microorganisms.[3] Today, risks from "recombinant DNA" research are considered to be much lower than originally estimated, and more specifically defined.[4]

B. *Patentability of Living Matter*

The issues of patentability that first confronted patent practitioners were more pedestrian, but acquired a certain cachet in the light of the intense public interest in the safety and morality debates. Whether a living organism was patentable subject matter under section 101 of the Patent Act[5] was a prominent issue. The Patent and Trademark Office (Patent Office) rejected two applications claiming a microorganism per se as if it were a device or a composition of matter.[6] The Court of Customs and Patent Appeals[7] held that the microorganisms were patentable subject matter.[8] The United States Supreme Court reviewed the lower courts' decisions and held that an invention was not unpatentable merely because it was alive.[9] The Supreme Court stated that the range of the patent laws was intended to encompass "anything under the sun that is made by man."[10] The Court, however, did not specify in which

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3. *Guidelines for Research Involving Recombinant DNA Molecules*, 51 Fed. Reg. 16,958 (1986)(listing the most current version of the guidelines). The National Institutes of Health is the major funding agency for biomedical research.

4. *See* ORGANIZATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT, RECOMBINANT DNA SAFETY CONSIDERATIONS (1986):

> Concern has been expressed that application of . . . rDNA organisms in the environment may present ecological risks, and attempts have been made to evaluate this potential for harm. . . . Past experience with species introduction have been studied in attempts to establish possible risks. In the great majority of instances no adverse consequences were noted.

Id. at 28.

5. Section 101 of the Patent Act provides that:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 101 (1988).

6. The Patent Office rejected the application of Malcolm E. Bergy for a biologically pure culture of the microorganism *streptomyces vellosus*. *In re* Bergy, 596 F.2d 952, 971 (C.C.P.A. 1979), *vacated as to Bergy sub nom.* Diamond v. Bergy, 444 U.S. 1028 (1980), *aff'd sub nom.* Diamond v. Chakrabarty, 447 U.S. 303 (1980). The Patent Office similarly rejected the application of Amanda M. Chakrabarty for a novel strain of oil-degrading *Psuedomonas*. *Id.* at 971.

7. Appellate jurisdiction for patent matters now resides in the United States Court of Appeals for the Federal Circuit. Federal Courts Improvement Act of 1982, Pub. L. No. 97-164, § 127(a), 96 Stat. 37 (codified as amended at 28 U.S.C. § 1295 (1988)).

8. *In re* Bergy, 596 F.2d at 973.

9. Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980).

10. *Id.* at 309 (citing S. REP. No. 1979, 82d Cong., 2d Sess. 5 (1952); H.R. REP. No. 1923, 82d Cong., 2d Sess. 6 (1952)). The same language was used in testimony by P.J. Federico regarding the 1952 Patent Act recodification legislation. *Id.* at 309 n.6. *See also, Hearings on H.R. 3760 Before Subcomm. No.3 of the House Comm. on the Judiciary*, 82d Cong., 1st Sess. 37 (1951).

category under section 101 microorganisms belonged.[11] This exercise of judicial restraint may ultimately prove most wise.

It is no coincidence that the patentability of living matter became an issue when it did. Microorganisms were in common use for producing antibiotics by fermentation since the 1950s. Patents for methods of synthesis using a specified microorganism strain were not uncommon. Vaccines made using microorganisms or containing killed or attenuated microorganisms were also the subject of patents. In fact, patents to organisms per se had already been granted.[12] The concept that the property of being alive could constitute a bar to patentability gained notoriety concurrently with the extensive public debate on the hazards of recombinant DNA and genetic engineering. The politics of the times generated this issue, abetted by misperceptions of the chemical and physical underpinnings of biological science. As one amicus curiae to the Chakrabarty Court pointed out, the issue before the Court constituted yet another last gasp of the vitalistic fallacy.[13] When viewed in this light, it is not only remarkable that the patentability of living matter became an issue, but also remarkable that the Supreme Court agreed to decide it.

Other cases interpreting the scope of patentable subject matter under section 101 in the context of other technologies also affected biotechnology patent law. In particular, *Parker v. Flook*[14] and several cases involving geophysical prospecting[15] dealt with inventions using information in the form of programs, algorithms, read-only memories, and other embodiments of information in combination with other process steps. DNA is a molecule that embodies genetic information, a read-only memory for programming biological systems. Consequently, the approaches taken in these cases also ultimately affected the direction of biotechnology patent law.

C. *Products of Nature*

Advances in biotechnology have also forced closer scrutiny of the "product of nature" rule. Statements in court opinions, often dicta, unsupported by statutory reference have fostered the misconception that all naturally occurring materials are unpatentable subject matter. The

11. 447 U.S. at 318. The categories under 35 U.S.C. § 101 include process, machine, manufacture, and composition of matter.

12. In a foresighted review, Edward S. Irons and Mary Helen Sears showed that the patentability of microorganisms was never questioned prior to the 1970s, despite numerous opportunities to do so. Irons & Sears, *Patents in Relation to Microbiology*, 29 ANN. REV. MICROBIOLOGY 319 (1975).

13. Brief for Dr. George Pieczenik as Amicus Curiae at 3-4, Diamond v. Chakrabarty, 447 U.S. 303 (1980)(No. 79-136). "To attempt to separate patentable and unpatentable subject matter on the basis of [living matter and non-living matter] is to invite confusion in the art, to ignore existing law and to ignore scientific reality." *Id.* at 3-4 (citations omitted).

14. 437 U.S. 584 (1978).

15. *In re* Sherwood, 613 F.2d 809 (C.C.P.A. 1980); *In re* Freeman, 573 F.2d 1237 (C.C.P.A. 1978); *In re* Johnson, 589 F.2d 1070 (C.C.P.A. 1978); *In re* Abrams, 188 F.2d 165 (C.C.P.A. 1951).

underlying policy is that what exists in nature is part of the public domain and therefore freely available to all.[16] In expressing the rule thus, the statutory underpinning for this argument would seem to be section 101[17] or section 102 of the Patent Act.[18] When the very existence of a natural compound is unknown before the inventor's activities, however, it strains logic to characterize the compound as not new or lacking novelty. Courts, persuaded by evidence of the technical value added by the inventor's activities, have held materials isolated and purified from nature patentable.[19] When human intervention has so altered the natural material from its natural state as to make it more useful, or useful in new ways, or cheaper, or available in greater quantity, the result is an addition to value over the natural state that merits patent protection. Viewing the natural state as prior art, the analysis of patentability of products of nature most logically proceeds under section 103.[20]

Many of the inventions in biotechnology involve materials purified from nature or otherwise manipulated from their natural state. Thus the cases interpreting the "product of nature rule" as an aspect of unobviousness have facilitated patent protection for biotechnology most significantly. As long as the fundamental criteria set forth in *Graham v. John Deere*[21] are met, valid claims to compounds isolated from a natural

16. *See, e.g.*, General Elec. Co. v. De Forest Radio Co., 28 F.2d 641, 642 (3d Cir. 1928), *cert. denied*, 278 U.S. 656 (1929)

> If it is a natural thing then clearly, even if [the patentee] was the first to uncover it and bring it into view, he cannot have a patent for it because a patent cannot be awarded for a discovery or for a product of nature, or for a chemical element.

(citing United States Indus. Chem. Co. v. Theroz Co., 25 F.2d 387 (4th Cir. 1928); Anheuser-Busch Ass'n v. United States, 207 U.S. 556, 562 (1908) (cork, without "having a distinctive name, character or use" held unpatentable)(citation omitted); Hartranft v. Wiegmann, 121 U.S. 609, 615 (1887)(shells that have not been manufactured into a new and different article held unpatentable).

17. 35 U.S.C. § 101 (product of nature is not "new").

18. 35 U.S.C. § 102 provides in part that a person shall be entitled to a patent unless:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States . . . .

35 U.S.C. § 102 (1988).

19. *See, e.g., In re* Bergy, 596 F.2d 952 (C.C.P.A. 1979), *vacated as to Bergy sub nom.* Diamond v. Bergy, 444 U.S. 1028 (1980), *aff'd sub nom.* Diamond v. Chakrabarty, 447 U.S. 303 (1980); *In re* Bergstrom, 427 F.2d 1394 (C.C.P.A. 1970); Merck & Co. v. Olin Mathieson Chem. Corp., 253 F.2d 156, 164 (4th Cir. 1958)(Compositions of "great therapeutic and commercial worth" are patentable where they are purifications of naturally occuring fermentates.).

20. Section 103 mandates that a patent be denied where:

> [T]he 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.

35 U.S.C. § 103 (1988).

21. 383 U.S. 1 (1966). According to the Court in *Graham*, an analysis of obviousness under section 103 must be based on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art at the time the invention was made; and (4) objective evidence of nonobviousness, if any. *Id.* at 17-18.

source, such as biological material, can be obtained. Examples of patentable products include cloned genes, DNA segments recombined in novel combinations, novel organisms possessing heterologous DNA, microorganisms isolated from natural sources, and purified proteins.

D. *Novelty*

Although biotechnology has experienced rapid and expansive progress, the field could not be characterized as crowded. Issues of anticipation under section 102[22] have not been encountered with great frequency. Those items which have been confronted could be categorized as matters of interpretation. *Scripps Clinic & Research Foundation, Inc. v. Genentech, Inc.*[23] suggests that a protein synthesized by recombinant means is anticipated by the naturally occurring protein in purified form. Patent examiners occasionally consider whether an unpurified mixture of DNA fragments sorted into vectors (a genomic or cDNA library[24]) anticipates a cloned gene. The rationale behind this is uncertain, since pure compounds are not deemed anticipated by impure mixtures.[25] Similar to the product of nature rule, such situations are best analyzed by determining how obvious the cloned gene would be to one skilled in the art, given knowledge of the library.

E. *Obviousness*

Due to the pioneering nature of many biotechnology inventions during the first seventeen years, issues of obviousness under section 103 have not been fully explored. The chemical structures of nucleic acids and proteins are so similar to one another that standard chemical analysis of monomer composition, molecular weight, viscosity and the like would lead to a conclusion of obviousness on structural criteria alone. Details of the sequences of nucleotides or of amino acids are the structural features that distinguish one nucleic acid or protein from another. The crucial distinguishing features are functional: how the compounds behave in biological systems, or how the compounds affect the behavior of biological systems themselves. Consequently, where sequence is an element of the disclosure, its main value, beyond proving novelty, is to help satisfy disclosure requirements.[26] No comprehensive theory relating chemical structure to biological function yet exists. Thus, if a biochemist develops a composition with novel structure and unobvious function, the Patent Office might consider the cloned DNA or purified

22. 35 U.S.C. § 102.

23. 666 F. Supp. 1379 (N.D. Cal. 1987).

24. For a definition of a genome and references that discuss genomic or cDNA libraries *see infra* note 49.

25. *See, e.g., In re* Bergstrom, 427 F.2d at 1401-02 ("[B]y definition, pure materials necessarily differ from *less* pure or impure materials and, if the latter are the only ones existing and available as a standard of reference . . . perforce the 'pure' materials are 'new' with respect to them.")(citation omitted); *In re* Cofer, 354 F.2d 664 (C.C.P.A. 1966); *In re* Seaborg, 328 F.2d 996 (C.C.P.A. 1964).

26. *See infra* note 34 and accompanying text.

protein unobvious. When the composition possesses a structure (sequence) similar to that possessed by a prior art compound and no new function or unobvious property can be shown, the standard of section 103 may not be met.[27]

Together, the recent cases of *In re Durden*[28] and *In re Pleuddemann*[29] have cast doubt on the unobviousness of processes where the only novel and unobvious element is the starting material. These cases do not expressly overrule prior cases that reached a contrary result,[30] making it unclear if a principle of law can be extracted from them. Many biotechnology process inventions could be affected by these decisions. Current efforts to clarify the situation by legislation are discussed elsewhere in this issue.[31]

Despite the fact that many biotechnology inventions could be considered pioneering, the "obvious to try" issue has been frequently raised, partly, because much of the prior art has been published academic work. *In re O'Farrell*[32] clarified the line between what is merely obvious to try and what is obvious. The applicants' published preliminary result was effective prior art against their own application. The claimed result was correct expression of a foreign gene in a recombinant host cell. The preliminary result was synthesis of an uncharacterized, high molecular weight protein using as the foreign "gene" a segment of DNA not known to encode a protein. In finding the invention obvious over the prior art, the court stated that "[o]bviousness does not require absolute predictability of success."[33] This case suggests that one crosses the line from "obvious to try" to "obvious" when the prior art discloses a crude version of the end result.

F. *Description and Enablement*

A variety of issues have arisen in the biotechnology art regarding description and enablement under section 112 of the Patent Act.[34] Many fall into the category of adequacy to support desired claim breadth, while others fall into the category of deposits of living organ-

27. For a discussion of the historical development of the obviousness question in chemical patents, how similarity in structure between a new compound and prior art leads to a *prima facie* case of obviousness, and how the current views of the Federal Circuit on this subject may impact the biotechnology field see Wall & Dituri, *The En Banc Rehearing of In re Dillon: Policy Considerations and Implications For Patent Prosecution*, 68 DEN. U.L. REV. 261 (1991)[hereinafter Wall & Dituri].

28. 763 F.2d 1406 (Fed. Cir. 1985).

29. 910 F.2d 823 (Fed. Cir. 1990).

30. *See, e.g., In re* Mancy, 499 F.2d 1289 (C.C.P.A. 1974).

31. Baechtold, *Property Rights in Living Matter: Is New Law Required?*, 68 DEN. U.L. REV. 141 (1991); Beir & Bensen, *Biotechnology Patent Protection Act*, 68 DEN. U.L. REV. 173 (1991).

32. 853 F.2d 894 (Fed. Cir. 1988).

33. *Id.* at 903.

34. To obtain a valid patent on a new, useful, and nonobvious invention, the patent applicant must file a specification fully disclosing the invention and how to make and use it. 35 U.S.C. § 112 (1982). Section 112 requires that the applicant describe three items: (1) the invention (the description requirement); (2) the manner and process of making and using the invention (the enablement requirement); and (3) the best mode contemplated by the inventor of carrying out his invention (the best mode requirement).

isms. The initial success of Cohen and Boyer in obtaining broad patent protection for a process that is the basic tool of the industry encouraged other pioneers in the field to hope for similar broad coverage. For a time, researchers feared that a number of broad blocking patents could limit opportunities for later entrants into the field. As the industry has grown, however, it now appears that problems of securing adequate claim breadth are more likely to be encountered.

Biotechnology is a field where functionally equivalent variants abound. Despite the fact that at critical loci a single base change in a nucleic acid sequence or a single amino acid substitution in a protein can drastically alter function, many non-critical loci occur which tolerate all sorts of sequence variations without affecting function. A claim limited to one sequence, or even half a dozen functionally equivalent sequence variants, is virtually worthless if a competitor can simply make another functional variant outside the claim. Given that literally thousands of functionally equivalent sequence variants exist, and that defining each of them is an impossible task (and useless since no new function is achieved thereby), practitioners have resorted to claiming a combination of sequence and function to obtain adequate claim coverage. Such claims, while they purport to be drawn to a family of compounds, take on the character of mechanical claims having means plus function language.[35] The case law relevant to the field of biotechnology is not limited to the field of chemical practice. Until the field develops its own body of precedents, precedents from other arts will be influential.

G. *Organism Deposits*

The practice of depositing a sample of a living organism in a public depository in order to comply with the requirements of section 112[36] is peculiar to biotechnology. This practice originated with making voluntary deposits to support process claims that used a specific novel microorganism strain. The deposit of the organism supplemented the written disclosure, where the specification could not describe how to make and use the microorganism.[37] In the late 1970s to mid-1980s, deposits were used extensively throughout the world.[38] With the Budapest Treaty,[39] an applicant could make a single deposit to satisfy the deposit require-

35. Adequate support for such claims must include teaching how to make and use functionally equivalent variants. Amgen, Inc. v. Chugai Pharmaceutical Co., Nos. 90-1273, -1275 (Fed. Cir. Mar. 5, 1991) (LEXIS, Genfed library, U.S. App. file 3481; WESTLAW, CTAF database 27262), *aff'g in part, rev'g in part, vacating in part* 13 U.S.P.Q.2d (BNA) 1737 (D. Mass. 1989).

36. 35 U.S.C. § 112.

37. *In re* Argoudelis, 434 F.2d 1390 (C.C.P.A. 1970).

38. *See* Winner & Denberg, *Requirements For Deposits of Biological Materials For Patents World Wide*, 68 DEN. U.L. REV. discussing (1991)[hereinafter Denberg & Winner](deposit requirements in various countries).

39. Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure, April 28, 1977, 32 U.S.T. 1243, T.I.A.S. No. 9768, 17 I.L.M. 285.

ment for any signatory country where the applicant's case was filed. The United States promulgated rules governing deposit practice in 1989.[40]

Upon issuance or publication, deposited materials must be available to the public. Applicants who are bound by this requirement do not favor it. For those who wish to enter the field, however, the deposit system is a boon, since they can avail themselves of the claimed organisms. The direct public access to the invention is unique to biotechnology. In other fields, public disclosure merely provides a set of instructions enabling competitors to reproduce the invention. Access to a deposited organism, however, short-cuts the need for sufficient skill to make the invention. The end product is placed directly into the hands of would-be competitors. Furthermore, such access is granted to anyone, even those not subject to United States law. The net effect is to encourage copying and counterfeiting. An applicant who must deposit materials to comply with section 112 has very little protection against such copying, short of infringement litigation.[41] Applicants who wish to avoid deposits must resort to trade secrets or provide a written disclosure teaching how to make the claimed organism from publicly available precursors. Lack of consistent standards among countries as to why a deposit is required and when it should be made results in added uncertainty for applicants.[42]

H. *Prosecution Delays*

A serious threat is presented by the infrastructural problems within the Patent Office. A recent report from the General Accounting Office stated that the backlog of biotechnology applications swelled by twenty-seven percent, from 6200 in January, 1989, to 7914 in May, 1989.[43] As a result, long delays occur, often as long as seven years, from the filing date to the issue date.[44] Despite the promulgation of new rules intended to resolve interferences within two years, cases are frequently suspended from prosecution for more than six months *before* an interference is declared. Litigants must frequently wait a year for decisions on preliminary motions.

Prosecution delays create incalculable consequences for the industry. As long as ownership rights remain unclear, companies continue to invest in research and development, and to introduce new products. By the time the patents issue, products are already in the market and litigation may be the only recourse. Litigation, interferences and even protracted prosecution are serious economic burdens, especially for small

40. 37 C.F.R. §§ 1.801-1.809 (1989).

41. The American Type Culture Collection will provide, for an additional fee, names of persons who have accessed the deposit. The applicant then has a basis for taking action against any infringer foolish enough to access the deposit in his own name.

42. *See generally* Denberg & Winner, *supra* note 38.

43. Andrews, *Long Delay Seen in Patents for Genetic Engineering*, N.Y. Times, July 19, 1990, at D1.

44. *See* Cohen & Boyer *supra* note 1. The parent Cohen-Boyer patent, for example, was pending for seven years before the first claim issued.

companies. Because most innovation takes place in smaller companies, the ultimate effect of the exaggerated costs and economic burden of procuring and enforcing patent protection is to stifle innovation rather than to promote it.

III. Prospective View

Turning to the next seventeen years, what trends can be projected and what hidden issues lie waiting to be exposed by the emergence of novel technology?[45]

A. *New Technologies*

Several recent developments in the biological sciences suggest new directions that may expand the scope of biotechnology. Recently, several papers have been published describing processes that open the door for new "biological" materials that have no counterpart in living organisms.[46] Novel proteins and nucleic acids can be developed by a combination of selection methods and specific amplification methods that yield molecules having a desired function. The ability to generate an endless number of new functions using variants of a single method will further emphasize the differences in rationale between chemical and biotechnology patent practice.

The technologies of the foregoing type will include a basic set of steps, modified only by varying a selection step. The starting material is the same—a pool of randomized sequences from which one having the desired *function* is ultimately isolated. Structure will not be predictable, however, the selected structure will be one of those present in the starting mixture. The method can isolate other structures having the same function, but those may have different sequences. While the structures would be patentable under conventional analysis as an unpredictable structure, once a technique for isolating structures having a particular function is known, other compounds with the same (equivalent) function can be generated. Techniques of this sort inherently possess means for generating a compound having a function. Similar to nonchemical inventions, such processes shift the emphasis from the structure of the resulting compound (sequence of amino acids or nucleotides), to its function. The same situation is reflected in existing technology where alternative functional sequences abound. The technological trend

45. No one understands better than a patent attorney the cruel disjunction of foresight and hindsight. That which is crystal clear after the fact is shrouded in fog beforehand. The following is offered with a painful sense that whatever is attempted as an exercise in foresight will have only entertainment value a few years hence. It may be that the author's prejudices, fears and wishful thinking also play a part.

46. Abelson, *Directed Evolution of Nucleic Acids by Independent Replication and Selection*, 249 Sci. 488 (1990); Devlin, Panganiban & Devlin, *Random Peptide Libraries: A Source of Specific Protein Binding Molecules*, 249 Sci. 404 (1990); Scott & Smith, *Searching for Peptide Ligands with an Epitope Library*, 249 Sci. 386 (1990); Tramontano, Janda & Lerner *Catalytic Antibodies*, 234 Sci. 1566 (1986); Tuerk & Gold, *Systematic Evolution of Ligands by Exponential Enrichment: RNA Ligands to Bacteriophage T4 DNA Polymerase*, 249 Sci. 505 (1990).

seems to be toward ever more predictable methodologies that permit those skilled in the art to attain alternative functional equivalents. As the trend progresses, chemical structure will become less important than function in patenting biological macromolecules. In this respect, biotechnology patent law may diverge from the precedents of chemical patent laws.

B. *Divergence from Chemical Patent Law*

The recent *en banc* reversal of *In re Dillon*[47] comes as a shock to biotechnology practitioners. The absolute primacy of *structural* relatedness as the key to establishing a prima facie case of obviousness seems misplaced in a field where structural similarity provides little guidance to functional properties. The relative unimportance of chemical structure in the biotechnology field suggests that *Dillon* should have little relevance. Misapplication of *Dillon* to biotechnological inventions has the potential to create considerable mischief.[48]

C. *Human Genome Project*[49]

The human genome project represents another area of biotechnology whose results may affect the development of biotechnology patent law. The process of mapping and sequencing the human genome is a

47. 919 F.2d 688 (Fed. Cir. 1990). For an in-depth analysis of the *en banc* rehearing of *Dillon*, see Wall & Dituri *supra* note 27.

48. At present, models of protein structure are not sufficiently developed to predict accurately three-dimensional configurations of a given sequence. The functional properties of a given amino acid sequence are almost never predictable from sequence alone. One can analyze sequence data in probability terms. Homologous sequences are more likely to have a common function than unrelated sequences. However, a single amino acid change at a critical locus can nullify the function, or can result in creating a new function. It is possible, through trial and error mapping experiments, to locate regions of sequence which tolerate a relatively wide range of sequence variation without affecting function. Through comparison of common functions in different sequences, certain sequence motifs are identifiable as associated with specific attributes. However, the level of predictability afforded by such information is rather crude, analogous to being able to identify which end of an automobile is the front. While the inventor of a novel protein may be unable to state from knowledge of its structure alone specifically which among thousands of possible sequence variants will retain equivalent function, he can predict with certainty that a very large number of such variants can easily be made. The same holds true for nucleic acids where redundant codings for identical amino acid sequences are known. Therefore, until a comprehensive understanding of structure-function relationships in biological systems is achieved, structural data are of value primarily to prove novelty and purity, but of little value to prove obviousness or to limit claim scope. *See* Wall & Dituri, *supra* note 27.

49. All living organisms are composed of cells, each no wider than a human hair. Each of our cells contains the same complement of DNA constituting the human genome. The DNA sequence of every person's genome is the blueprint for his or her development from a single cell to a complex, integrated organism that is composed of more than 10^{13} (10 million million) cells.

NATIONAL RESEARCH COUNCIL COMMITTEE ON MAPPING AND SEQUENCING THE HUMAN GENOME, MAPPING AND SEQUENCING THE HUMAN GENOME 12 (1988). Currently there is no single human genome project, instead there are many projects in both the public and private sectors. Among the objectives of the genome projects are to create maps of human chromosomes consisting of DNA markers that would permit scientists to locate genes quickly, and to determine the DNA sequence of a large fraction of the human genome and that of other organisms. OFFICE OF TECHNOLOGY ASSESSMENT, MAPPING OUR GENES GENOME PROJECTS: HOW BIG, HOW FAST 6-7 (1988).

departure from traditional avenues of scientific inquiry. Segments of human DNA will be cloned and sequenced without concomitant information regarding the function. An enormous amount of position and sequence data will be added to the databases, often without correlated information of associated functional properties.[50] The prior art effect of such data is difficult to predict. It remains an open question whether *Dillon* is applicable where the prior art reveals only structure, with no hint of functional properties. The debate in *Dillon* over the relative significance of "structure" and "properties" as factors in establishing a prima facie case of obviousness can be expected to continue. The results, however, may be different in the biotechnology field than in the chemical field.[51]

D. *Transgenic Animals*

The next seventeen years will witness an exponential increase in the kinds of transgenic animals created. The parameters of patentability for transgenics are currently unknown. Both genotype (the structure of the introduced gene and its control elements) and phenotype (the characteristics of the transgenic animal attributable to the introduced gene) are key features of a transgenic animal that serve to characterize it and to distinguish it from the prior art. The question of which of these features is more significant to determine obviousness or to establish a prima facie case of obviousness is likely to occupy examiners, practitioners, and the courts for some years. The parallel to the debate over "structure" versus "properties" in the chemical field is inescapable.[52]

The problems of patent enforcement for self-replicating products are likely to be particularly serious for products sold in a mass market. For patent holders, the prospect of extending transgenic animal technology to agriculture presents unusual problems. Congress has proposed special legislation that would provide exemptions for farmers, permitting them to breed and sell patented transgenic animals without

50. Much of the data may be in the form of partial sequences, specifically just enough sequence at the ends of a cloned segment to allow the same segment to be reisolated from a library by polymerase chain reaction, using the disclosed sequences as primers. *See* Appenzeller, *Democratizing the DNA Sequence*, 247 SCI. 1030 (1990); Roberts, *New Game Plan for Genome Mapping*, 245 SCI. 1438 (1989).

51. When doing research, the chemist's attention is generally directed first toward the structure of a compound and second toward determining its functional properties. In biotechnology, the reverse is most often the case: research is directed initially toward finding a compound having a particular function, then secondarily to elucidating its structure. Within the epistemologies of the two sciences, the relative significance of structure and properties are quite different. Therefore, the law affecting these two fields of art is likely to reflect this dichotomy.

52. The kinds of questions which could arise are numerous. If the gene introduced into mouse A differs only in its promoter from that introduced into mouse B, is A unobvious in view of B on the ground that the phenotypes of A and B are unpredictably distinct? If the gene introduced into mouse A yields a characterized phenotype, are rat A, dog A, horse A, etc., each having the same gene and phenotype obvious in view of mouse A? Will mouse A', having the same phenotype as mouse A but a slightly different introduced gene, infringe a claim to mouse A? Is a claim to mouse A overly broad if the gene construct is recited in terms of equivalent sequences rather than limited to a specific sequence?

infringement.[53] Underlying such legislation is the fear that effective patent protection for valuable farm breeding stock might dislocate farm economics in socially unfavorable ways.[54] Whether such dislocations would occur and whether legislation of the sort proposed would have the effects desired by its sponsors may become a matter of political debate.

E. *Internationalization*

In addition to legal issues driven by new science, there are issues generated by changes in business economics, and by current political and legal trends. The internationalization of commercial enterprise and the increasing worldwide interdependence of national economies creates pressure to develop a more uniform set of national patent laws. Talks leading to a Patent Harmonization Treaty have been in progress over the past few years.[55] The prospects for successful internationalization are encouraged by the strength and quality of the European Patent Convention.[56] The pros and cons for the United States patent system presented by the Patent Harmonization Treaty have been discussed by many commentators.[57] As a practical matter, the international character of the modern market economy is such that even small businesses must take into account foreign laws governing patentability and enforcement.[58] The present trend toward increasing harmonization and standardization of patent laws seems likely to continue.

The nationalistic view of patents as a means to protect local proprietary interests is being displaced by a view of patents as a means of providing world-wide proprietary rights, regardless of the invention's origin.[59] If the United States adopts a first-to-file system, interferences

53. Transgenic Animal Patent Reform Act, H.R. 4970, 100th Cong., 2d Sess. (1988) (The statute proposed exemptions for farmers with gross incomes of less than $500,000, or are single family farmers, or farmers who do not engage in the growing of animals for sale.).

54. *See* H.R. REP. No. 888, 100th Cong., 2d Sess., at 72 (1988).

55. *See* H.R. CON. RES. 354, 101st Cong., 2d Sess., 136 CONG. REC. 94, H5198, E2425 (daily ed. July 20, 1990)(statement of Rep. Porter); *Summary of Proceedings at Special Meeting of the Membership on Harmonization on Patent Law*, ABA SEC. OF PAT., TRADEMARK AND COPYRIGHT L., September 9, 10, 1989, at 83 (1990); *Interference Issues in a First-to-File World*, 18 A.I.P.L.A. Q.J. No. 1 (1990).

56. European Patent Convention, art. 93, (1973), *reprinted in* 78 PAT. & TRADEMARK REV. 31, 39 (1980).

57. *See* sources cited *supra* note 55.

58. Activities which do not bar patentability in the United States, such as public disclosure within one year of the patent filing date, can defeat patentability in most other countries. Small businesses and academic inventors sometimes fail to consider the effects of such disclosures on patent rights outside the United States, to their increasing detriment. Small businesses increasingly look to foreign markets and academic inventors increasingly seek industrial funding for which world-wide patent rights are a common consideration. In the absence of a formal harmonization treaty, a kind of street harmonization exists in which the most restrictive provisions of the laws of each relevant jurisdiction are observed.

59. The trend is uneven, being more pronounced in the more industrialized countries with strong orientation toward a market economy, weaker in less developed countries where developing a local industrial-technical base has a high priority.

will eventually be phased out, although oppositions may come to occupy a substantial part of the practitioner's docket. Canada has abandoned its first-to-invent system for a first-to-file system.[60] Although changes occur with glacial slowness in the international patent arena, the prospect of an international patent agency, along the lines pioneered by the European Patent Office, providing a unified patent enforceable throughout the industrialized world is entirely feasible by the end of the next seventeen years.

F. *Infringement, Equivalence, Claim Interpretation*

While issues of patentability have been dominant in the first patent lifetime, issues of infringement, equivalence and claim interpretation[61] may come to dominate the second. Issues of fact, such as whether an accused organism is identical to a claimed organism, may entail amassing significant amounts of evidence to be resolved. By the end of the next patent term, the body of case law on equivalence and reverse equivalence is likely to be greatly expanded in breadth and sophistication.[62] Indeed, many terms used in biotechnology claims, while definable in ways that reasonable people would consider clear, may require resort to an equivalence type of analysis when litigants are involved.

G. *Patent Judiciary*

The composition of the judiciary may be affected by the growing number of practitioners and patent examiners that have advanced degrees in science. In both the examining corps and the practicing bar, the number of persons with Ph.D.s or Master's degrees in a biotechnology-related discipline[63] has increased in response to the technical demands of the subject matter.[64] A familiarity with scientific language and practices ought to be as valuable in court as a familiarity with business practices and terminology. Both administrative and judicial decision making may be enhanced. The infusion of a greater degree of scientific knowledge into decision making, both in patent law and in general law, will be a side benefit of the growth of biotechnology.

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60. The Patent Act, CAN. REV. STAT. ch. p-4, § 27 (1985), *amended by* ch. 33, § 8 (3rd Supp. 1987) (As a result of this amendment the United States and the Philippines are the only remaining countries with a first-to-invent system.).

61. *See* Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 608 (1950)("[A] patentee may invoke this doctrine [of equivalents] to proceed against the producer of a device 'if it performs substantially the same function in substantially the same way to obtain the same result.' ").

62. *See* Genentech, Inc. v. The Wellcome Found. Ltd., 14 U.S.P.Q.2d (BNA) 1363 (D. Del. 1990)(Denying summary judgment in a biotechnology patent infringement action brought by Genentech against Wellcome, the judge found a triable issue of fact concerning whether the patented compound and infringing compound performed in substantially the same way.).

63. Biotechnology-related disciplines include physics, chemistry, microbiology, biochemistry, genetics or molecular biology and physiology.

64. That some of these will eventually complete the transit from lab bench to judicial bench should be a healthy trend provided their legal qualifications are the primary selection criteria.

IV. Concluding Summary

The existing precedents, based primarily in the chemistry field, served adequately during the early development of biotechnology. Major threshold questions of patentability, relative to living organisms and products of nature, are now largely resolved. The courts now accept products of biotechnology as patentable subject matter, subject to the same statutory criteria of novelty, unobviousness, description and enablement as inventions in other fields. Applying the statutory criteria to the facts of biotechnology inventions is an ongoing process, whose outlines in the case law are only beginning to take shape. As biotechnology patent practice matures, it is being viewed less as a direct descendant of chemical practice than as a cousin. The body of biotechnology precedents is expected to take on a more individualistic character separate from chemical practice and drawing from precedents in other arts as well.

The future will be characterized by further definition of a body of biotechnology case law, which in turn will be affected by new technologies that further accent differences between biotechnology practice and chemical practice. General trends toward internationalization of business and harmonization of patent laws can be expected to bring about more uniform treatment of biotechnology in patent systems around the world.