News and Comment

Patents for Life Forms *sui generis*: Some New Questions for Science, Law and Society*

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This essay examines the Supreme Court ruling on the patentability of microorganisms and the attendant problems of the novelty, identity and ownership of life forms.

Introduction

The Supreme Court decision in the case *Chakrabarty v. Diamond* issued on June 16, 1980 resolves an eight year controversy over whether the right to patent protection, as provided by the Constitution and federal laws, includes life forms *per se*. In 1972, A.N. Chakrabarty filed an application on behalf of the General Electric Company to patent a strain of *Pseudomonas* bearing multiple plasmids, each with a specific hydrocarbon degradative capacity. The application was initially denied by the Patent and Trademark Office (PTO) on the grounds that (i) the extant laws made no provision for patenting life forms *per se*, except as stipulated by Congress in special legislation for plants, and (ii) the microorganisms in question are "products of nature."

The ruling was upheld by the PTO Board of Appeals, but subsequently reversed by the Court of Customs and Patent Appeals before it was brought before the Supreme Court.

Although the technique that Chakrabarty used to develop the modified *Pseudomonas* strain did not involve recombinant DNA methods, the decision is viewed as having its most significant impact on the commercial applications of this research technology.[1]

This essay reviews the principal argument addressed to the Court and examines some new problems that arise out of the decision which upholds patentability of self-propagating microorganisms *sui generis*.

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Chakrabarty's Invention

Chakrabarty started out with the strain *Pseudomonas aeruginosa*, which possesses no special properties for degrading any of the hydrocarbons present in crude oils. Aided by natural processes of DNA exchange (conjugation), he then transferred four plasmids into the *Pseudomonas* strain. Each of the plasmids has the capability of degrading one of the essential hydrocarbons in crude oil (N-octane, camphor, salicylate and naphthalene). The final product was presented as a new strain of *Pseudomonas* which could not be found in nature and was uniquely suited for degrading the four principal components of crude oil. Chakrabarty offered the following description of how the new bacterium would function:

> In practice an inoculum of dry (or freeze-dried) powders of these genetically engineered microbes will be dispersed over (e.g. from overhead) an oil spill as soon as possible to control spreading of the oil.... A particularly beneficial manner of depositing the inoculum on the oil spill is to impregnate straw with the inoculum and drop the inoculated straw on the oil spill where both components will be put to use—the inoculum (mass of microbes) to degrade the oil and the straw to act as a carrier for the microbes and also to function as an oil absorbant.[2]

The patent claims for this organism were of three types: (i) the method of producing the bacterium, (ii) the process of administering the bacterium to an oil spill, and (iii) the bacterium *per se*. It was the third claim that was rejected by the PTO and the Board of Appeals. The patent rights for the method of constructing the organism, the method of isolating or purifying it, or of its use in a particular process were not contested.

In some cases there is not much to gain by holding a patent on an organism *per se* in contrast to a process. But if the organism has a multiplicity of uses, not all of which can be initially specified, controlling it outright does offer additional protection to its "inventor." Consider as examples, a broad spectrum vector (bacteriophage or animal virus) or an engineered bacterium which can transport foreign gene products to its surface membrane, allowing for more efficient extraction of the proteins.

The scope of Chakrabarty's patent claim went beyond the four plasmid bacterium. The application was for "a bacterium from the genus *Pseudomonas* containing therein at least two stable energy-generating plasmids each of said plasmids providing a separate hydrocarbon degrada-

ble pathway." Thus, although the petitioner has not developed an eight plasmid bearing strain, if the patent application is granted, such a hypothetical organism would be included in the scope of the claim.

The Arguments

The cardinal objection by the PTO to granting a patent was that the rearrangement of genetic materials and modification of life forms does not qualify the substance as a manufacture or new composition of matter. In question was the interpretation of the language in a single paragraph from 35 U.S.C., section 101:

> 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.

The PTO argued that (i) there is no "clear and certain sign from Congress that any living organisms, much less microorganisms," are patentable under section 101; (ii) Congress took special initiative in passing the Plant Patent Act of 1930 and the Plant Variety Protection Act of 1970 to extend patient protection to certain species of plants—evidence to support point (i).

In contrast, General Electric and its *amici* maintained that Chakrabarty's oil degrading bacteria was a manufactured entity. For example, in its *amicus curiae* brief, the University of California cited language previously issued by the Court for a manufacture.[3] It stated that there must be transformation whereby a new and different article must emerge having a distinctive name, character or use. Chakrabarty maintained that his organism satisfies this criterion. Moreover, he argued that Congress did not intend to exclude living organisms form patent opportunities; the exclusion only applied to natural entities, be they living or inert.

The Supreme Court's Decision

The Supreme Court decided the Chakrabarty case in a 5 to 4 vote.[4] Speaking for the majority, Chief Justice Warren Burger held that new constellations of living matter are no less products of manufacture than rearrangements of inert substances. The relevant distinction for patenting, Burger concluded, is not whether the artifact is living or dead, but whether it is a product of nature or a human-made invention. The majority found no ambiguity in the language of 35 U.S.C. with respect to patenting living matter *per se*, notwithstanding the passage of the plant patent acts.

As far as any adverse social consequences of genetic engineering that may arise out of the patenting of life forms, the Court held that it is not the competent body to consider the arguments. "That process involves the balancing of competing values and interests, which in our democratic system is the business of elected representatives.[5]

While the Chakrabarty case puts to rest one issue, many new problems have emerged which eventually will be resolved by legal precedent or congressional action.

To begin with, let us consider the question of progeny rights for a patented microorganism. Imagine that a patented bacterium escapes a commercial facility or university laboratory and establishes itself in a public space. It is then picked up by someone who wishes to use the organism for commercial purposes in ways distinctly different from its present use by the patent holder. Does the patent holder have entitlements over the way that the progeny of the microorganism is used? Except for the initial "manufacture," human intervention plays no role in subsequent replications of the organism. Are each of the daughter cells to be considered a product of manufacture? Without such coverage there may be no point in patenting life forms *sui generis*. Companies would more likely seek protection of their products through trade secrets if patents do not secure rights over all potential uses and for all progeny of the organism. On the other hand, an organism found in the environment may be a million generations from its manufactured parentage. If patents cover the progeny of life forms, that is tantamount to the private ownership of the forms of biological reproduction.

The Novelty of Life Forms

Among the open-ended questions that the PTO and the courts will be saddled with is: how much novelty must be induced in a living organism to qualify it as a product of manufacture?

With diminishing sources of funding and rapidly rising operating costs to contend with, universities are seeking to place under patent any experimental organisms that might conceivably have commercial value. Scientific investigators are expected to cooperate. Until there is sufficient experience from which to draw generalities or until guiding principles are developed, litigation will establish policy as institutions begin the rush to stake out patent claims. Meanwhile, some of the salient questions for ascertaining novelty are: Has the organism been found in nature or is there a reasonable likelihood that it could be? Could the organism survive in nature or has its modification made it unstable? Can the organism produce a product, transfer DNA, or alter the environment in a unique way?

Patent applications have been filed for biologically pure cultures produced from a mass of soil microorganisms. This was argued in *Parker v.*

Bergy. The petitioner claimed to have produced a pure culture of *Streptomyces vellosus* which is used for the production of the antibiotic lincomycin. The PTO ruled against the patent on the grounds that the subject matter was a product of nature. The Board of Appeals sustained the rejection, but on grounds that a living organism is not a patentable subject matter. The Court of Customs and Patent Appeals (CCPA) issued a reversal, both on the grounds raised by the PTO and the Board of Appeals. However, the CCPA expressed some reservation that a product of nature was before it. Bergy's case was withdrawn before it reached the Supreme Court. Thus, there is still some disagreement over whether and to what degree a pure isolate of a mass of undifferentiated organisms found in nature is patentable and qualifies as a "composition of matter."

Fingerprinting Organisms

The patent laws require an inventor to describe the object or process in clear and exact terms, precise enough to allow someone skilled in the area to reproduce the results. As a consequence of the difficulties in differentiating plant varieties in precise language, the provision for product specification was modified in the Plant Patent Act of 1930 to permit descriptions which were to be as concrete *as reasonably possible*. It is reasonable to assume that this provision would be equally important for the microbes themselves.

Since 1949, the deposit of cell cultures in public depositories, such as the Northern Regional Research Laboratory of the Department of Agriculture or the American Type Culture Collection, has become an important requirement in the patenting process. Once a patent is granted, a sample of the culture becomes available to others for research purposes. Anticipating a substantial increase in patent requests in the wake of the Supreme Court's ruling, there has been some interest in creating a single national depository. Its function would be to provide a uniform system of fingerprinting culture types and to offer more effective coordination of U.S. depositories with those of other countries.

The patentability of organisms raises the importance of the description requirement for biological inventions. The patent is for the life form independent of its use, and therefore a greater burden is placed on establishing its genetic identity. How is the organism to be fingerprinted? For a bacterium it will certainly be something less than the map of the entire genome (including plasmids). More than likely, decriptions will depend on the state of the art. Contested patents will also encourage refinements of description. Initially, we might expect bacterial identity to be determined through a combination of conventional taxonomic indicators with the addition of the novel genetic sequences which have been added. The PTO will have to deal with minor mutations and trivial sequence changes decribed in subsequent patent claims.

Bacterial Products

The patent rights to an organism *per se* covers any commercial uses to which it can conceivably be put. A question arises when one of the by-products of a bacterium is found in nature. Human insulin is obviously found in nature but is not available in sufficient quantities for clinical use. One might guess that the patent for a human insulin-producing bacterium does not carry with it the rights over human insulin. If it did, there could be no other product of human insulin, by whatever method and using whatever other organism, until the patent period had expired. But the issue will undoubtedly become more complicated.

Let us suppose that the by-product of our patented organism is a substance that, while present in nature, is purer than anything that either (i) presently exists, or (ii) can presently be extracted from the natural environment. Interferon is a case in point. Does the patent holder of the interferon-producing bacterium lay claim to the product and preclude others from manufacturing the same substance through other techniques—assuming that the purity of the product has been adequately established? Kiley has argued that the comparative ease and affordability of extraction of products like interferon should be factors in granting a patent on the substance itself.[6]

On a related issue, a legal battle over the commercial ownership rights to a life form has developed between the University of California at Los Angeles and the New Jersey pharmaceutical company, Hoffman-La Roche. Roche wants a federal court to determine whether it can file a patent claim on a line of interferon-producing cells that were first isolated by UCLA scientists. At stake in the litigation is the estimated 3 billion dollar interferon market.[7]

Species Barriers and Patents

Several years ago Robert Sinsheimer postulated that eukaryotic and prokaryotic organisms were separated by an evolutionary barrier that blocked the natural exchange of genetic information between species.[8 9] The argument was linked to Sinsheimer's concern that the transgression of such barriers could upset an evolutionary balance or produce new strains of pathogenic organisms.

Sinsheimer's arguments were countered by Bernard Davis,[10] who offered an argument from natural selection for why such barriers do not exist, and Cohen and Chang,[11] who ran an experiment to test the barrier hypothesis. Both Davis and the Cohen-Chang team argued that it is highly

likely that bacteria have been taking up eukaryotic DNA, albeit at a low frequency and with poor chance of survival.

Is there a contradiction within patent law in holding that nature has already tried what is being accomplished through gene splicing and that the recombinant organisms are novel and therefore patentable entities? Some see no problem in holding both propositions. They maintain that nature's failures must be distinguishable from nature's successes. According to this view, bacteria which may have taken up DNA from higher order cells, but which have been selected against, cannot serve as a standard for determining what is a product of manufacture. The argument continues: If the organism can survive in nature in a form that can be extracted and isolated, then, and only then, is a laboratory duplication of it not a manufacture. The legal resolution of this issue may rest less on the theory of natural selection than with the evidence that the life form in question is sufficiently distinct in function, morphology and ecology from its progenitor organism.

Multicellular Organisms

No principle of law, in any of the arguments brought before the Supreme Court in *Chakrabarty*, implies that patentability be restricted to monocellular organisms. If one cell can be a "manufacture," then why not eight? Why not a fertilized egg or an embryo? And what about an animal line? Scientists can clone frogs and will soon be able to clone other species. Will we soon see patent requests for genetic strains of animals in a manner analogous to what is presently being done with plants? To take a patent out on an animal one must presumably show that it is a product of manufacture. Here is one set of hypothetical conditions that might satisfy the requirements:

1. A patent is granted on a fertilized egg after the genome has been engineered to qualify as a "manufacture."

2. The egg is developed into a viable multicellular organism for either insertion into a host for gestation or *in vitro* growth.

3. The legal framework is in place for extending the patent rights of animal cells to that of the mature organism.

If patented germ plasm is available in large enough quantity, then conceivably entire herds may fall under patent protection. Furthermore, if patent protection extends to the progeny, then multiple generations of selected animals can be owned for the duration of the patent.

Some nations have established a demarcation between microorganisms and higher life forms for the purpose of patent rights. The European patent convention and the German Patent Act exclude plant and animal varieties from patent protection.[12]

Conclusion

The Supreme Court acknowledged that its decision was made on a fine point of law. "Our task, rather, is the narrow one of determining what Congress is free to amend [section] 101 as to exclude once that is done our powers are exhausted. Congress if free to amend [section] 101 as to exclude from patent protection organisms produced by genetic engineering."[13]

Some have interpreted the Court's language as a tacit invitation for Congress to act. Thus far there is no indication that Congress intends to restrict patents of life forms in any way. As biotechnology moves from the research laboratory to the commercial field, genetic engineering is being viewed by the financial community and the government as one of the new hopes for the reindustrialization of the American economy.[14] And any restriction on the patent rights of inventors, according to some, would foster the decline of America's lead in technological innovation.[15]

The granting of patents, which originates in the Constitution, gives Congress the authority "to promote the progress of science and useful arts by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries...."[16] The protection of inventions is offered by society at the expense of establishing a limited monopoly. The patent forces disclosure of the product or process but eliminates competitive production. There have been instances where Congress has excluded certain innovative technologies from patentability, as in the case of the production of fissionable materials and the utilization of atomic energy. But the exceptions are rare.

For academic biology, the Court's decision will undoubtedly have an effect on the flow of scientific information. At this early stage, however, it is difficult to tell whether the overall impact of university patents and industrial-university linkages will enhance or diminish cooperation among scientists. It is also premature to ascertain whether the commercial sector will choose the patent route as against that of maintaining trade secrets. But one outcome of the *Chakrabarty* decision is undisputed: it has created a vast fertile ground for future litigation.

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[1]Harold M. Schmeck, Jr., "U.S. to process 100 applications for patents on living organisms," *New York Times*, June 18, 1980.

[2]Cited in *Parker v. Bergy, Chakrabarty*, Brief of U.S. Patent & Trademark Office to Court of Customs & Patent Appeals, October 1978, 32-33.

[3]Regents of the University of California. Brief *amicus curiae*. to U.S Supreme Court in *Diamond v. Chakrabarty*. 79-136. p. 13.

[4]Supreme Court Decision. Re: *Diamond v. Chakrabarty*. *U.S. Law Week* 48:4714-19 (June 16. 1980).

[5]*Ibid*.. 4718

[6]Thomas D. Kiley. "Learning to live with the living invention," *Amer. Patent Law Assoc. Quart.* 7(3&4):220-235 (1979).

[7]*European Chemical News*. vol. 34 (April 14. 1980).

[8]Robert L. Sinsheimer. "Troubled dawn for genetic engineering." *New Scientist* 68:148-151 (October 16. 1977).

[9]Robert L. Sinsheimer. "An evolutionary perspective for genetic engineering," *New Scientist* 73:150-152 (January 30. 1977).

[10]Bernard Davis. "The recombinant DNA scenarios: Andromeda strain. chimera and golem." *American Scientist* 65:547-555 (September/October 1977).

[11]Shing Chang and Stanley N. Cohen. "*In vivo* site-specific genetic recombination promoted by the Eco RI restriction endonuclease." *Proc. Nat'l Acad. Sci.* 74:4811-4815 (November 1977).

[12]Franz Lederer. "A perspective in patenting microorganisms under the European convention: prospects and considerations," *Amer. Patent Law Assoc. Quart.* 7(3&4):296 (1979).

[13]*Law Week*. 4718.

[14]See opening statement by Adelai Stevenson in "Industrial applications of recombinant DNA techniques." *Hearings before the Subcommittee on Science. Technology. and Space*. May 20. 1980. Washington: U.S. Gov't. Print. Off., 1980, 1-2.

[15]The point was made by the New York Patent Law Association in their *amicus curiae* brief in *Diamond v. Chakrabarty*. p. 7.

[16]U.S. Constitution. Art. I. Sec. 8.

The Role of the Food and Drug Administration in the Regulation of the Products of Recombinant DNA Technology*

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Introduction

The statutory mandate of the Food and Drug Administration (FDA) provides authority to regulate products accounting for 25 cents of every consumer dollar. Because of the wide scope of our regulatory authority, we expect to play a role in reviewing and approving for marketing many of the products of recombinant DNA technology.

We would like here to offer our perspectives on:

1. Those products regulated by FDA expected to be produced by recombinant DNA technology in the near future;

2. How applications for product approval that involve recombinant DNA technology will be reviewed; and

3. What we currently see as our larger societal responsibilities for regulating a technology that has aroused considerable public interest and concern and yet holds great commercial and therapeutic promise.

The Products

Many products regulated by FDA are expected to be produced in the near future by recombinant DNA technology. Our own assessment indicates that among those falling under the regulatory purview of our various Bureaus are:

1. Drugs—human insulin, human growth hormone, thymosin, ACTH, other peptide hormones, endorphins (if they show therapeutic potential), and DNA itself.

2. Biologics—interferon, vaccines (such as hepatitis B and influenza), DNA, serum albumin, coagulation factors and other blood components, including urokinase.

3. Veterinary medicine—bovine growth hormone and interferon.

4. Foods—certain enzymes used in food processing.

5. Medical Devices—*in vitro* diagnostic tests (e.g., glucose oxidase); specific antenatal tests for thalassemia and sickle cell anemia.

The Regulatory Process(es)

How will applications for product approval that involve recombinant DNA technology be reviewed? Congress has provided FDA authority under the Food Drug and Cosmetic (FD&C) Act and Public Health Service (PHS) Act to regulate products regardless of how they are manufactured.

We recount below the requirements for each product class before approval of a product for marketing. Each product of recombinant DNA technology must meet all the appropriate existing statutory requirements:

1. Drugs—The FD&C Act defines new drugs as those not generally recognized by qualified scientific experts as safe and effective. New drugs may not be marketed unless they have been approved as safe and effective, and clinical investigations on human subjects by qualified experts are prerequisite for determination of safety and effectiveness. Sponsors of investigations of new drugs or

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