

Chapter 5

COMMERCIALIZATION OF GENETIC RESEARCH: PROPERTY, PATENTS, AND CONFLICTS OF INTEREST

I. INTRODUCTION

The framers of the U.S. Constitution realized that it was important to create incentives for technological innovation. The U.S. Constitution, Art. 1, § 8, cl. 8 provides: "Congress shall have the power ... To promote the progress of science and ... the useful arts, by securing for limited times to ... inventors the exclusive right to their ... discoveries."

Under the federal patent statute, inventors are rewarded with a 20 year period of exclusivity that forbids anyone else from making, using, selling or offering to sell their invention in order to make sure that novel, useful, and nonobvious technologies get developed that otherwise might not have been created.

Without the exclusive protection provided by a patent, individual inventors and institutions would not be willing to invest time and money in creating new products. Their research and development efforts could be too easily undermined if a competitor could use their work to introduce a duplicate product without the prior investment of resources. Since the development of a drug and its testing on research subjects generally involves hundreds of millions of dollars, patent protection is particularly important to the pharmaceutical industry.

A patent application spells out the processes, composition of matter, and other inventions being protected. It describes the invention and how to make it. In order to obtain a patent, the invention must be "novel." It cannot have been publicly described more than a year earlier in, for example, a scientific journal or at a professional meeting. It must be "nonobvious"—that is, people skilled in the field at issue must not think the invention is a trivial advance. (If there is a patent on a red ball, an inventor would not be able to obtain a patent on a yellow ball.) The

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patent must be "useful." An inventor cannot patent a new chemical, for example, unless it has a particular beneficial use.

The patent application must be adequately "enabling" as well. That is, it must describe the invention fully, in a way that would allow another person skilled in that field to make the invention. This requirement is particularly important since one of the purposes of the patent law is to assure that the public gets information back in exchange for the monopoly granted to the patent holder. When a patent is granted, the information in it becomes public. Other inventors can then use that information to further their own research. Other inventors, however, cannot make or use the patented invention or process itself without the permission of the patent holder.

Typically, a gene patent claims to cover a purified and isolated gene, the protein for which the gene codes, cells or biological entities that have been engineered to express the gene, the process by which the gene was purified, and the use of the gene or protein to detect or treat a disease or condition. In January 2001, the U.S. Patent and Trademark Office, which has the statutory authority to grant or deny patent applications, issued new guidelines clarifying the usefulness criteria in the context of patents involving DNA. The utility of the invention to be patented must be specific, substantial, and credible. "The Patent Office's new rules with more stringent requirements on real-world use for gene patents will help keep squatters from just putting their name on genes and hoping it will be come valuable," Todd Dickinson, the Patent Office's Director, told a Congressional hearing. "One simply cannot patent a gene itself without also clearly disclosing a use to which that gene can be put," he said. For example, raw DNA sequence data, such as that generated by the Human Genome Project, is not patentable.

When a company is issued a gene patent, it gains exclusive rights to commercialize the patented gene. Most companies' primary method of commercially exploiting patented genes is through agreements in which they license others to use their patents. An example of such an agreement would be a company charging a per test fee to doctors to use sequence information about the company's patented gene to identify whether a patient has a mutation in that gene. Licensing agreements can also be created that allow other researchers to conduct research involving patented genes. These licenses may take one of two forms. The license may charge a royalty for the use of the gene in research to create another product (such as a diagnostic test or a gene therapy). Or the license may include a reach-through agreement where the patent holder earns a percentage of the profits from the ultimate sales of other products that licensees created through research on the patented gene. For example, a company could enter an arrangement to receive a set percentage of gross sales from a gene therapy developed using its patented gene. A company is also free to prevent others from using its patented gene. The company can then develop commercial products utilizing its patented gene and enjoy the monopoly on those products that a gene patent provides.

There is much controversy regarding whether genes should be patentable under existing laws. The U.S. Patent and Trademark Office has determined that a genetic sequence can be patented if the patent applicant can describe that sequence and its function. But the U.S. Supreme Court has not ruled on the issue of whether genes fall within the statutory definition of patentable subject matter. And Congress itself maintains the power to eliminate gene patents if legislators were convinced that they excessively inhibit research or substantially interfere with patient care. In some quarters, there are arguments that genes should be viewed as part of the common heritage of humankind and not subject to ownership as a form of intellectual property.

The patenting of genes has led to legal questions about the type of informed consent that should be obtained from the person whose bodily tissue has been used to isolate a gene. Additional questions are raised about whether the person (or groups) whose genetic material has been patented should share in the proceeds. Vast sums of money are at stake. The patent related to the human erythropoietin gene (which codes for a protein needed by kidney disease patients) is worth more than \$1.5 billion a year because a genetically engineered treatment can be made from it.

Concerns have been raised about the increasing focus on patenting and commercializing genetic discoveries within university and government molecular biology laboratories. Prior to the 1980s, government researchers and academic researchers funded by the government generally could not personally profit commercially from their research. Federal technology transfer laws changed that by allowing taxpayer-funded researchers to patent their inventions and form or contract with for-profit companies to exploit them.

Researchers with commercial interests—who are now the majority in the genetics field—sometimes protect their interests in ways that are fundamentally changing the nature of science. They keep information confidential that they once readily shared. There is also evidence that the sharing of research materials is decreasing. Scientists with access to biological materials from patients are now less likely to give samples of those materials to other researchers. This is true even with genes and cell lines, where replication techniques can create millions of copies of the genes or cells and thus sharing does not diminish the first scientist's ability to carry out research. Other researchers have reported difficulty in accessing research tools—such as gene segments—developed through taxpayer-funded research at the National Institutes of Health. There are questions about whether this approach will best serve society in the long run.

HUGO + SNP Consortium
are trying to stop
this

**U.S. DEPARTMENT OF ENERGY OFFICE OF SCIENCE,
OFFICE OF BIOLOGICAL AND ENVIRONMENTAL
RESEARCH, HUMAN GENOME PROGRAM**

<http://www.ornl.gov/hgmis/elsi/patents.html>

GENETICS AND PATENTING

What are patents, and how do they work?

The patentability of inventions under U.S. law is determined by the Patent and Trademark Office (USPTO) in the Department of Commerce. A patent application is judged on four criteria. The invention must be "useful" in a practical sense (the inventor must identify some useful purpose for it), "novel" (i.e., not known or used before the filing), and "nonobvious" (i.e., not an improvement easily made by someone trained in the relevant area). The invention also must be described in sufficient detail to enable one skilled in the field to use it for the stated purpose (sometimes called the "enablement" criterion).

In general, raw products of nature are not patentable. It's usually when these DNA products have been isolated, purified, or modified to produce a unique form not found in nature that they become patentable.

The USPTO has 3 years to issue a patent. In Europe, the timeframe is 18 months. The USPTO is adopting a similar system. Patents are good for 20 years from filing date.

In the United States, patent priority is based on the "first to invent" principle: whoever made the invention first (and can prove it) is awarded property rights for the 20-year period. Inventors have a one-year grace period to file after they publish. All other countries except the Philippines, however, follow a "first inventor to file" rule in establishing priority when granting patents.

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Currently over three million genome-related patent applications have been filed.... Those who use sequences from public databases today risk facing a future injunction if those sequences turn out to be patented by a private company on the basis of previously filed patent applications.

*Patenting Genes, Gene Fragments, SNPs,
Gene Tests, and Proteins*

In terms of genetics, inventors must

- (1) identify novel genetic sequences,
- (2) specify the sequence's product,
- (3) specify how the product functions in nature—i.e. its use
- (4) enable one skilled in the field to use the sequence for its stated purpose

Genes and Gene Fragments

USPTO has issued a few patents for gene fragments. Full sequence and function often are not known for gene fragments. On pending applications, their utility has been identified by such vague definitions as providing scientific probes to help find a gene or another EST or to help map a chromosome. Questions have arisen over the issue of when, from discovery to development into useful products, exclusive right to genes could be claimed.

The 300- to 500-base gene fragments, called expressed sequence tags (ESTs), represent only 10 to 30% of the average cDNA and the genomic genes are often 10 to 20 times larger than the cDNA. A cDNA molecule is a laboratory-made version of a gene that contains only its information-rich (exon) regions; these molecules provide a way for genome researchers to fast-forward through the genome to biologically important areas. The original chromosomal locations and biological functions of the full genes identified by ESTs are unknown in most cases.

Patent applications for such gene fragments have sparked controversy among scientists, many of whom have urged the USPTO not to grant broad patents in this early stage of human genome research to applicants who have neither characterized the genes nor determined their functions and uses.

In December 1999, the USPTO issued stiffer interim guidelines stating that more usefulness must now be shown before gene fragments are considered patentable—specifically how the product functions in nature. The new rules call for “specific and substantial utility that is credible,” but some still feel the rules are too lax.

The patenting of gene fragments is controversial. Some say that patenting such discoveries is inappropriate because the effort to find any given EST is small compared with the work of isolating and characterizing a gene and gene product, finding out what it does, and developing a commercial product. They feel that allowing holders of such “gatekeeper” patents to exercise undue control over the commercial fruits of genome research would be unfair. Similarly, allowing multiple patents on different parts of the same genome sequence—say on a gene fragment, the gene, and the protein—adds undue costs to the researcher who wants to examine the sequence. Not only does the researcher have to pay each patent holder via licensing for the opportunity to study the sequence, he also has to pay his own staff to research the different patents and determine which are applicable to the area of the genome he wants to study.

SNPs

Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A,T,C,or G) in the genome sequence is altered. For example a SNP might change the DNA sequence AAGGCTAA to ATGGCTAA. SNPs occur every 100 to 1000 bases along the 3-billion-base human genome. SNPs can occur in both coding (gene) and noncoding regions of the genome. Many SNPs have no effect on cell function, but scientists believe others could predispose people to disease or influence their response to a drug.

Variations in DNA sequence can have a major impact on how humans respond to disease; environmental insults such as bacteria, viruses, toxins, and chemicals; and drugs and other therapies. This makes SNPs of great value for biomedical research and for developing pharmaceutical products or medical diagnostics. Scientists believe SNP maps will help them identify the multiple genes associated with such complex diseases as cancer, diabetes, vascular disease, and some forms of mental illness. These associations are difficult to establish with conventional gene-hunting methods because a single altered gene may make only a small contribution to the disease.

In April 1999, ten large pharmaceutical companies and the U.K. Wellcome Trust philanthropy announced the establishment of a non-profit foundation to find and map 300,000 common SNPs. Their goal is to generate a widely accepted, high-quality, extensive, publicly available map using SNPs as markers evenly distributed throughout the human genome. The consortium plans to patent all the SNPs found, but they will not enforce the patents. This will be done only as a measure to

prevent others from patenting the same information. Information found by the consortium is being made freely available via NIH's NCBI public Database of Single Nucleotide Polymorphisms.

Gene Tests

As disease genes are found, complementary gene tests are developed to screen for the gene in humans who suspect they may be at risk for developing the disease. These tests are usually patented and licensed by the owners of the disease gene patent. Royalties are due the patent holder each time the tests are administered, and only licensed entities can conduct the tests.

Pros

Cons

DIAMOND v. CHAKRABARTY

447 U.S. 303 (1980).

BURGER, J.

We granted certiorari to determine whether a live, human-made micro-organism is patentable subject matter under 35 U.S.C. § 101.

I.

In 1972, respondent Chakrabarty, a microbiologist, filed a patent application, assigned to the General Electric Co. The application asserted 36 claims related to Chakrabarty's invention of "a bacterium from the genus *Pseudomonas* containing therein at least two stable energy-generating plasmids, each of said plasmids providing a separate hydrocarbon degradative pathway." This human-made, genetically engineered bacterium is capable of breaking down multiple components of crude oil. Because of this property, which is possessed by no naturally occurring bacteria, Chakrabarty's invention is believed to have significant value for the treatment of oil spills.

* * *

The patent examiner ... rejected claims for the bacteria. His decision rested on two grounds: (1) that micro-organisms are "products of nature," and (2) that as living things they are not patentable subject matter under 35 U.S.C. § 101.

Chakrabarty appealed the rejection of these claims to the Patent Office Board of Appeals, and the Board affirmed the Examiner on the second ground. Relying on the legislative history of the 1930 Plant Patent Act, in which Congress extended patent protection to certain asexually reproduced plants, the Board concluded that § 101 was not intended to cover living things such as these laboratory created micro-organisms.

The Court of Customs and Patent Appeals, by a divided vote, reversed on the authority of its prior decision in *In re Bergy*, 563 F.2d 1031, 1038 (1977), which held that "the fact that microorganisms ... are alive ... [is] without legal significance" for purposes of the patent law.

II.

The Constitution grants Congress broad power to legislate 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." Art. I, § 8, cl. 8. The patent laws promote this progress by offering inventors exclusive rights for a limited period as an incentive for their inventiveness and research efforts.

IS IT
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The question before us in this case is a narrow one of statutory interpretation requiring us to construe 35 U.S.C. § 101, which provides:

"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."

Specifically, we must determine whether respondent's micro-organism constitutes a "manufacture" or "composition of matter" within the meaning of the statute.

III.

* * *

"[C]omposition of matter" has been construed consistent with its common usage to include "all compositions of two or more substances and ... all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids." . . .

The relevant legislative history also supports a broad construction. The Patent Act of 1793, authored by Thomas Jefferson, defined statutory subject matter as "any new and useful art, machine, manufacture, or composition of matter, or any new or useful improvement [thereof]." The Committee Reports accompanying the 1952 Act inform us that Congress intended statutory subject matter to "include anything under the sun that is made by man."

This is not to suggest that § 101 has no limits or that it embraces every discovery. The laws of nature, physical phenomena, and abstract ideas have been held not patentable. Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none."

Judged in this light, respondent's micro-organism plainly qualifies as patentable subject matter. His claim is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity "having a distinctive name, character [and] use." The point is underscored dramatically

by comparison of the invention here with that in *Funk* [Brothers Seed Co. v. Kalo Inoculant Co., 333 U.S. 127 (1948)]. There, the patentee had discovered that there existed in nature certain species of root-nodule bacteria which did not exert a mutually inhibitive effect on each other. He used that discovery to produce a mixed culture capable of inoculating the seeds of leguminous plants. Concluding that the patentee had discovered "only some of the handiwork of nature," the Court ruled the product nonpatentable.

* * *

Here, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101.

* * *

Congress is free to amend § 101 so as to exclude from patent protection organisms produced by genetic engineering. Cf. 42 U.S.C. § 2181(a), exempting from patent protection inventions "useful solely in the utilization of special nuclear material or atomic energy in an atomic weapon." Or it may choose to craft a statute specifically designed for such living things. But, until Congress takes such action, this Court must construe the language of § 101 as it is.

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BRENNAN, J., WHITE, J., MARSHALL, J., and POWELL, J. join, dissenting.

* * *

The sweeping language of the Patent Act of 1793, as re-enacted in 1952, is not the last pronouncement Congress has made in this area. In 1930 Congress enacted the Plant Patent Act affording patent protection to developers of certain asexually reproduced plants. In 1970 Congress enacted the Plant Variety Protection Act to extend protection to certain new plant varieties capable of sexual reproduction. Thus, we are not dealing—as the Court would have it—with the routine problem of "unanticipated inventions." In these two Acts Congress has addressed the general problem of patenting animate inventions and has chosen carefully limited language granting protection to some kinds of discoveries, but specifically excluding others. These Acts strongly evidence a congressional limitation that excludes bacteria from patentability.

First, the Acts evidence Congress' understanding, at least since 1930, that § 101 does not include living organisms. If newly developed living organisms not naturally occurring had been patentable under § 101, the plants included in the scope of the 1930 and 1970 Acts could have been patented without new legislation. Those plants, like the bacteria involved in this case, were new varieties not naturally occurring.

* * *

Congress plainly has legislated in the belief that § 101 does not encompass living organisms. It is the role of Congress, not this Court, to broaden or narrow the reach of the patent laws. This is especially true where, as here, the composition sought to be patented uniquely implicates matters of public concern.

AMGEN, INC. v. CHUGAI PHARMACEUTICAL CO., LTD.

927 F.2d 1200 (Fed.Cir.1991).

LOURIE, J.

This appeal and cross appeal ... involve issues of patent validity, infringement, and inequitable conduct with respect to ... U.S. Patent 4,703,008 ('008), owned by Kirin-Amgen Inc. (Amgen),....

Chugai Pharmaceutical Co., Ltd. (Chugai) and Genetics Institute, Inc. [GI] (collectively defendants) assert on appeal that the district court erred in holding that: 1) Amgen's '008 patent is not invalid under 35 U.S.C. §§ 102(g) and 103; 2) the '008 patent is enforceable; 3) the failure of Amgen to deposit the best mode host cells was not a violation of the best mode requirement under 35 U.S.C. § 112....

* * *

Erythropoietin (EPO) is a protein consisting of 165 amino acids which stimulates the production of red blood cells. It is therefore a useful therapeutic agent in the treatment of anemias or blood disorders characterized by low or defective bone marrow production of red blood cells.

The preparation of EPO products generally has been accomplished through the concentration and purification of urine from both healthy individuals and those exhibiting high EPO levels. A new technique for producing EPO is recombinant DNA technology in which EPO is produced from cell cultures into which genetically-engineered vectors containing the EPO gene have been introduced. The production of EPO by recombinant technology involves expressing an EPO gene through the same processes that occur in a natural cell.

* * *

U.S. Patent 4,703,008, entitled "DNA Sequences Encoding Erythropoietin" (the '008 patent), [was] issued on October 27, 1987 to Dr. Fu-Kuen Lin, an employee of Amgen. The claims of the '008 patent cover purified and isolated DNA sequences encoding erythropoietin and host cells transformed or transfected with a DNA sequence. [In 1983, Dr. Lin "obtained the amino acid sequence for EPO and designed two sets of probes to isolate the EPO gene from a 'genomic library,' a mixture containing most, if not all, of the human genes," making Amgen the first biotechnology company to clone the EPO gene. In July 1984, Dr. Edward Fritsch, of GI, isolated the EPO gene using a very similar technique. "GI does not contest that Dr. Lin was the first actually to clone the gene, but, among other things, argues that Dr. Fritsch invented the methodology necessary to clone the gene in December, 1981 before Dr. Lin

Cancer, too

Amgen
DNA
reference

Chugai Pharm
Technique

conceived of it and that by 1983 Dr. Lin's methodology was obvious." Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd., 13 U.S.P.Q.2D (BNA) 1737, (D.Mass.1989).]

* * *

The first issue we review is whether the district court erred in finding that the claims directed to a purified and isolated DNA sequence encoding human EPO were not invalidated by the work of GI's Dr. Fritsch. Section 102(g) provides in relevant part that:

A person is entitled to a patent unless—(g) before the applicant's invention thereof the invention was made . . . by another who had not abandoned, suppressed, or concealed it. In determining priority of invention there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

* * *

The invention recited in claim 2 is a "purified and isolated DNA sequence" encoding human EPO. The structure of this DNA sequence was unknown until 1983, when the gene was cloned by Lin; Fritsch was unaware of it until 1984. As Dr. Sadler, an expert for GI, testified in his deposition: "You have to clone it first to get the sequence." In order to design a set of degenerate probes, one of which will hybridize with a particular gene, the amino acid sequence, or a portion thereof, of the protein of interest must be known. Prior to 1983, the amino acid sequence for EPO was uncertain, and in some positions the sequence envisioned was incorrect. Thus, until Fritsch had a complete mental conception of a purified and isolated DNA sequence encoding EPO and a method for its preparation, in which the precise identity of the sequence is envisioned, or in terms of other characteristics sufficient to distinguish it from other genes, all he had was an objective to make an invention which he could not then adequately describe or define.

A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, e.g., encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.

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Fritsch had a goal of obtaining the isolated EPO gene, whatever its identity, and even had an idea of a possible method of obtaining it, but he did not conceive a purified and isolated DNA sequence encoding EPO and a viable method for obtaining it until after Lin. It is important to recognize that neither Fritsch nor Lin invented EPO or the EPO gene. The subject matter of claim 2 was the novel *purified and isolated* sequence which codes for EPO, and neither Fritsch nor Lin knew the structure or physical characteristics of it and had a viable method of obtaining that subject matter until it was actually obtained and characterized.

* * *

As expert testimony from both sides indicated, success in cloning the EPO gene was not assured until the gene was in fact isolated and its sequence known. Based on the uncertainties of the method and lack of information concerning the amino acid sequence of the EPO protein, the trial court was correct in concluding that neither party had an adequate conception of the DNA sequence until reduction to practice had been achieved; Lin was first to accomplish that goal.

* * *

Defendants contend that "in the field of living materials such as microorganisms and cell cultures," we should require a biological deposit so that the public has access to exactly the best mode contemplated by the inventor. This presents us with a question of first impression concerning the best mode requirement for patents involving novel genetically-engineered biological subject matter.

For many years, it has been customary for patent applicants to place microorganism samples in a public depository when such a sample is necessary to carry out a claimed invention.... Such a deposit has been considered adequate to satisfy the *enablement* requirement of 35 U.S.C. § 112, when a written description alone would not place the invention in the hands of the public and physical possession of a unique biological material is required.

* * *

[W]hen, as is the case here, the organism is created by insertion of genetic material into a cell obtained from generally available sources, then all that is required is a description of the best mode and an adequate description of the means of carrying out the invention, not deposit of the cells. If the cells can be prepared without undue experimentation from known materials, based on the description in the patent specification, a deposit is not required. Since the court found that that is the case here, we therefore hold that there is no failure to comply with the best mode requirement for lack of a deposit of the CHO cells, when the *best mode* of preparing the cells has been disclosed and the best mode

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Public
depository

cells have been enabled, *i.e.*, they can be prepared by one skilled in the art from known materials using the description in the specification.

* * *

Amgen argues that the district court's holding that GI "provided clear and convincing evidence that the patent specification is insufficient to enable one of ordinary skill in the art to make and use the invention claimed in claim 7 [a purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake] of the '008 patent without undue experimentation" constituted legal error. Amgen specifically argues that the district court erred because it "did not properly address the factors which this court has held must be considered in determining lack of enablement based on assertion of undue experimentation."

Claim 7 is a generic claim, covering all possible DNA sequences that will encode any polypeptide having an amino acid sequence "sufficiently duplicative" of EPO to possess the property of increasing production of red blood cells. As claims 8, 23-27, and 29, dependent on claim 7, are not separately argued, and are of similar scope, they stand or fall with claim 7.

* * *

That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. The essential question here is whether the scope of enablement of claim 7 is as broad as the scope of the claim.

* * *

Moreover, it is not necessary that a patent applicant test all the embodiments of his invention; what is necessary is that he provide a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of his claims. For DNA sequences, that means disclosing how to make and use enough sequences to justify grant of the claims sought. Amgen has not done that here.... What is relevant depends on the facts, and the facts here are that Amgen has not enabled preparation of DNA sequences sufficient to support its all-encompassing claims.

It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently to meet the requirements of Section 112. Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim

encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them.

In affirming the district court's invalidation of claims 7, 8, 23-27, and 29 under Section 112, we do not intend to imply that generic claims to genetic sequences cannot be valid where they are of a scope appropriate to the invention disclosed by an applicant. That is not the case here, where Amgen has claimed every possible analog of a gene containing about 4,000 nucleotides, with a disclosure only of how to make EPO and a very few analogs.

* * *

Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112.