EXHIBIT 7

Chapter 3
The Structure of the Marketplace

INTRODUCTION

A therapeutic product, such as a biologic, becomes available in the health care marketplace after many years of developing and researching the product, testingit for safety and efficacy in humans and animals, gaining marketing approval from the Food and Drug Administration(FDA), and finally developing a process for distributing and marketing it to health care professionals and facilities.

This chapter describes the history of the development, production, and marketing of recombinant erythropoietin in the United States. A complex set of legal and regulatory forces are shaping the recombinant erythropoietin marketplace, including biotechnology patent issues, orphan product designations, and licensing agreements among the various manufacturers. Based on this information, this chapter discusses the supply side of the market for recombinant erythropoietin. The final sections of the chapter outline arrangements for distributing the biologic and discuss sources of demand for dialysis patients and others.

HISTORY OF DISCOVERY AND PRODUCTION

erythropoietin is an amino acid glycoprotein hormone that is produced by the kidneys and liver in humans and animals[1](102). Although the medical significance of erythropoietin has long been recognized, a process to produce sufficient quantities of pure erythropoietin for therapeutic purposes had eluded scientists for almost 80 years.

It was first postulated in 1906 that erythropoietin was the natural molecule responsible for the regulation and control of red blood cell production in the body (116,137). In 1957, it was discovered that erythropoietin was produced by the kidneys and that the anemia of chronic renal disease was caused, at least in part, by deficiency of this renal hormone (76).

Extended medical research on erythropoietin was minimal, however, because of its scarce availability from natural sources and the lack of a technique that could sufficiently purify the compound for human administration. Attempts to isolate and purify erythropoietin from various sources yielded unstable, biologically inactive preparations of the hormone.

Milestones in the development of recombinant erythropoietin are listed in table 3-1. A major breakthrough for the potential production of erythropoietin for therapeutic use occurred in 1977, when scientists developed a technique that isolated and highly purified erythropoietin from the urine of severely anemic patients (102). Although the purification technique itself did not provide sufficient material for therapeutic use, it lead to subsequent work using genetic engineering.

In the 1980s, several biotechnology manufacturers simultaneously pursued strategies to develop processes to produce recombinant erythropoietin for therapeutic use. These included Amgen Inc. of Thousand Oaks, California and Genetics Institute of Cambridge, Massachusetts.

Amgen and Genetics Institute utilized biotechnology to develop a process to produce recombinant erythropoietin for therapeutic use. Biotechnology is the application of biological systems to technical and industrial processes. It has been defined as any technique that uses living organisms or parts of living organisms to make or modify products, to improve plants or animals, or to develop microorganisms for specific use (148). Biotechnology is now commonly used by many industrial sectors, including plant agriculture, hazardous waste management, and human therapeutics. In the pharmaceutical field it can be substituted for conventional methods of making new therapeutic entities by cloning cells that produce human compounds and by producing large quantities of scarce compounds. Pharmaceuticals made through biotechnology are usually classified into one of three categories: those that affect the immune system, those that mediate human tissue repair, and those that correct metabolic defects or alter metab-

[1]Although the kidney is the major producer of exythropoietin, about 10-15 percent is produced by the liver (63).

Table 3-I-Milestones in the Development of Recombinant Erythropoietin

Date	Milestone
1977	Scientists discover a process that produce highly spurified erythropoietin, but a process for producing significant quantities of the compound is still unavailable.
1983	Amgen clones the gene for human erythropoietin.
1984	Amgen and Kirin Brewery of Japan enter into a licensing agreement for recombinant erythropoietin.
1984	Genetics Institute and Chugai Pharmaceuticals of Japan enter into a licensing agreement for erythropoietin.
Nov. 30, 1984	Amgen applies for patent covering its cell line that produces recombinant erythropoietin in Chinese hamster ovary (CHO) cells.
January 1985	Genetics Institute applies for patents covering erythropoietin and recombinant erythropoietin.
Sept. 30, 1985	Amgen and Ortho enter into licensing agreement for recombinant erythropoietin.
Oct. 8, 1985	Genetics Institute and Boehringer-Mannheim enter into a licensing agreement for recombinant erythropoietin in European markets.
April 1986	Amgen receives orphan drug designation for use of recombinant erythropoietin for anemia associated with ESRD.
June 30, 1987	Genetics Institute patent granted.
August 1987	Ortho receives orphan drug designation for use of recombinant erythropoietin for anemia associated with ESRD.
October 1987	Chugai Pharmaceuticals of Japan receives orphan drug designation for use of recombinant erythropoietin for anemia associated with ESRD.
Oct. 27,1987	Amgen's patent granted.
November 1987	Amgen files a PLA and ELA with the FDA for use of recombinant erythropoietin for anemia associated with ESRD.
May 17, 1988	Chugai Pharmaceuticals of Japan and Upjohn Company of Kalamazoo, Michigan form Chugai-Upjohn of Rosemont, Illinois.
July 1988	Ortho receives orphan drug designation for use of recombinant erythropoietin for anemia of preterm infancy.
September 1988	Chugai-Upjohn files a PLA and ELA with FDA for use of erythropoietin for anemia associated with chronic renal failure.
February 1989	Ortho files a PLA and ELA for use of recombinant erythropoietin for anemia associated with chronic renal failure and for infection or treatment of human immonodeficiency virus (HIV).
March 1989	Ortho receives orphan drug designation for use of recombinant erythropoietin for anemia associated with HIV infection or treatment.
June 1,1989	FDA approves Amgen's PLA and ELA for use of recombinant erythropoietin (Epoetin alfa) for anemia associated with chronic renal failure.
October 1989	FDA informs Amgen that it has 7 years of market exclusivity for use of Epoetin alfa in anemia of chronic renal failure (retroactive to June 1, 1989)*.
December 1989	Boston court rules that central claims of Amgen's and Genetics Institute's recombinant erythropoietin patents are valid, and certain other parts are invalid.
March 15,1990	Boston court orders Genetics Institute and Amgen to submit royalty-free cross-licensing agreement to court within 60 days and resolve dispute over orphan product designations.

*Amgen originally filed a PLA for the use of recombinant erythropoietin in the anemia of End Stage Renal Disease (ESRD). At the request of the FDA, and prior to approval, this indication was expanded to chronic renal failure. The Office of Orphan Products Development then awarded orphan drug status to Amgen's Epoetin alfa for the broader indication of chronic renal failure (142).

KEY: ELA = establishment licensing application; PLA = product licensing application; ESRD = end stage renal disease.

SOURCE: Office of Technology Assessment, 1990.

olism unrelated to the immune system. Recombinant erythropoictin is classified as a recombinant product for tissue repair, since replacement of red blood cells is considered tissue regeneration (15).

The aspect of pharmaceutical biotechnology that Amgen used to make recombinant erythropoietin is genetic engineering, which is defined as the purposeful manipulation of an organism's deoxyribonucleic acid (DNA) or hereditary material.[2] Genetic engineering of recombinant erythropoietin is a multistage operation requiring identification of the gene that produces erythropoietin, isolation of the gene, replication of the gene in an easily manipulated microorganism, production of recombinant erythropoietin, and purification of recombinant erythropoietin in a stable, biologically active form (15). Large-scale production of recombinant erythropoietin was accomplished through insertion of the human erythropoietin gene into Chinese hamster ovary (CHO) cells, which were then able to produce recombinant erythropoietin (160).

Amgen entered into several licensing agreements with other pharmaceutical manufacturers for recombinant erythropoietin, as indicated in table 3-2.[3] For example, it licensed its recombinant erythropoietin rights in Japan to the Kirin Brewery in 1984. It also entered into a licensing agreement in 1985 with the Ortho Pharmaceutical Corporation, in Raritan, New Jersey, a subsidiary of Johnson and Johnson (166). Under the provisions of this agreement with Ortho, Amgen retained the U.S. marketing rights to recombinant erythropoietin for anemia associated with chronic renal failure in individuals requiring dialysis, and Ortho obtained recombinant erythropoietin marketing rights for all other indications in the United States, including anemia associated with chronic renal failure for individuals who do not yet require dialysis (predialysis). Ortho also gained the rights to all uses of recombinant erythropoietin in foreign markets other than Japan and China.[4]

Table 3-2-Recombinant erythropoietin Marketing Rights

Company holding patent	Region	Company holding distribution/ marketing rights
Amgen Inc.	USA (dialysis)	Amgen Inc.
	USA (non-dialysis)	Ortho Pharmaceutical
	Japan	Kirin Brewery
	Europe	Ortho Pharmaceutical
Genetics Institute	USA	Chugai-Upjohn
	Japan	Chugai Pharmaceuticals
	Europe	Boehringer-Manheim

SOURCE: Retterson, 1989 (117); Sobota, 1990 (132).

Building on the 1977 purification technique breakthrough, Genetics Institute developed a method for producing erythropoietin in 1984. Genetics Institute licensed its erythropoietin product rights to the Chugai Pharmaceutical Company in Japan and to the Boehringer-Mannheim Company in Europe (127). In order to sell recombinant erythropoietin in the United States, Chugai Pharmaceuticals of Japan entered into a cooperative marketing agreement in May 1988 with a major pharmaceutical manufacturer, the Upjohn Company of Kalamazoo, Michigan, to form the Chugai-Upjohn Company, based in Rosemont, Illinois (see table 3-2).

The next steps in bringing recombinant erythropoietin to market were for the manufacturers to test the safety and efficacy of the product in animals and humans and to submit the required data to FDA for approval to market the product.

2 DNA is the molecule in chromosomes that is the repository of genetic information in all organisms (with the exception of a small number of viruses in which the hereditary material is **ribonucleic** acid, known as RNA). The information coded by DNA determines the structure and function of an organism.

3 In the **legal** context, a license is written authority granted by the owner of a patent to another party empowering the latter to make or use the patented article for a limited period of time or in a limited territory (14). In a licensing agreement, a pharmaceutical manufacturer usually sells its rights to produce and market a product or specific uses of a product to another manufacturer in return for a fee and a royalty arrangement based on sales of the product.

4 In March 1990, **Amgen** and **Ortho** were involved in binding arbitration to settle disputes related to their 1985 licensing agreement.

FDA APPROVAL OF RECOMBINANT erythropoietin

In order for a prescription drug or biologic to be marketed in interstate commerce in the United States, it must have FDA approval. A biologic is defined as any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of humans (21 CFR 600.3h).

The FDA approval process for new therapeutic products, including biologics, involves a lengthy, complex, and rigorous series of tests for safety and efficacy (21 CFR 601.25dl). After tests in laboratory animals indicate that a compound may have therapeutic value in humans, three phases of clinical trials are required prior to FDA approval (21 CFR 312.21).

Phase I trials involve the participation of a small number of healthy volunteers or patients to determine the safety of the product and appropriate dosing ranges and intervals? The data obtained in this phase should be used to design well-controlled, scientifically valid studies in later phases. Phase II trials include controlled clinical studies that involve the participation of patients who have the disease the product is supposed to treat. The purpose of these studies is to determine the initial efficacy of the product, dosing parameters in diseased patients, and how the agent is metabolized and excreted by the human body. Phase III trials include a series of controlled and uncontrolled studies in which a total of several hundred to several thousand patients are administered the product to gather additional information about efficacy and safety. Phase III studies also determine whether the product produces a broader range of adverse effects than those detected in the smaller Phase I and II studies. An additional series of studies, known as Phase IV studies, may be undertaken after the product is marketed to determine long-term adverse effects that may not have been detected during the first three phases.

After the first three phases of clinical studies for a biologic are completed, the manufacturer submits a product Licensing Application (PLA) and Establishment Licensing Application (ELA) to the FDA. A biologic cannot be marketed unless a PLA and ELA are both approved by FDA. PLA approval is based on safety and efficacy data generated from the clinical trials. ELA approval is based on inspection and certification by FDA personnel that the facilities in which the biologic is to be produced are in compliance with FDA's definition of good manufacturing practices (21 CFR 601.10b).[6]

Amgen's PLA and ELA for the use of recombinant erythropoietin for anemia associated with end-stage renal disease (ESRD) were submitted to FDA in October 1987 and approved June 1, 1989.[7] FDA, however, approved the product for use in the broader population of chronic renal failure, of which ESRD is a subset.[8] The brand name for Amgen's product is Epogen.

Ortho submitted a PLA and ELA to FDA in February 1989 for recombinant erythropoietin for anemia associated with chronic renal failure and for the anemia associated with human immunodeficiency virus (HIV) infection and treatment (l). FDA has not yet approved either application. The brand name for Ortho's product is Eprex (174).

Chugai-Upjohn submitted a PLA and ELA for its recombinant erythropoietin in September 1988, and neither has yet been approved (l). Chugai-Upjohn is

5 The number of participants required for each phase of clinical trials depends on the numbers necessary to achieve sufficient statistical power.

6 According to regulations, licenses for the maintenance of establishments for the manufacture and preparation of biologics may be issued only upon showing that the establishment and the products meet standards designed to ensure the continued safety, purity, and potency of the products (42 USC 201).

I An inspection of the Amgen production facility was conducted by the Center for Biologics Evaluation and Research on January 9-11,1989 (160).

8 FDA reasoned that ESRD is one phase along the continuum known as chronic renal failure, and that chronic renal failure is the more global term which adequately describes the spectrum of renal insufficiency. Patients who are being dialyzed and patients who are not being dialyzed may both be anemic and may require transfusions, and with the development of recombinant erythropoietin, may be candidates for treatment with the product (159).

seeking FDA-approval for the use of recombinant erythropoietin for anemia associated with chronic renal failure (l), and will use Marogen as the trade name for its product (132).

FDA developed a nomenclature to distinguish among the potential recombinant erythropoietin products of the various manufacturers. The term epoetin is to be used for recombinant erythropoietin, and a modifier, such as alfa, beta, gamma, etc., will be added to identify the products of the various manufacturers approved by the FDA (160). Therefore, since Amgen's recombinant erythropoietin was the first to be FDA approved, it is known as Epoetin alfa. The next manufacturer's product to be approved by the FDA, if any, would be known as Epoetin beta.[9]

RECOMBINANT erythropoietin AND PATENT DISPUTES

Under the applicable U.S. laws, a patent maybe issued to cover "any new useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." (35 USC 101). The patentability of new synthetic pharmaceutical entities is well established in the U.S. legal system. The patent is a major mechanism by which pharmaceutical manufacturers protect their investment in research and development. Prior to 1980, the U.S. patent office held that living organisms were products of nature and outside the scope of the office's statutory subject matter. Based on this reasoning, the office did not grant patents on such products (148). This situation changed with a 1980 landmark Supreme Court decision, Diamond vs. Charkabarty, in which the Court ruled that live, microorganisms made by humans were patentable (477 USC *303, 1980).*

Uncertainty surrounding the actual protection that a patent gives to biotechnology products continues to present potential barriers to further innovation and commercialization in this industry (148). The patent disputes that have developed among Amgen, Chugai, and Genetics Institute are an indication of the complexity and uncertainty of the biotechnology patent law field.

On October 27, 1987, Amgen received a patent on the intermediate product that is used to make recombinant erythropoietin in CHO cells. It applied for the patent on November 30, 1984.[10] Genetics Institute received a patent on homogeneous erythropoietin on June 30, 1987. It applied for the patent on January 11, 1985.[11] Also in January 1985, Genetics Institute filed for a patent on recombinant erythropoietin analogous to Amgen's. Amgen, Chugai, and Genetics Institute are all using recombinant technology to produce recombinant erythropoietin in Chinese hamster ovary cells (48).

In October 1987, in a suit filed against both Genetics Institute and Chugai Pharmaceutical, Amgen claimed that the companies were infringing on its recombinant erythropoietin patent. Genetics Institute and Chugai Pharmaceutical counter sued Amgen on the same grounds. In a complex decision, a Boston court ruled in December 1989 that certain claims of each patent were valid, but that other parts of each patent were invalid (6). The court concluded that each manufacturer was infringing on parts of the

9 According to the upcoming edition of the ***United States Adopted Names and the United States Pharmacopeia Dictionary of Drug Names,*** **Amgen's** product has been designated **Epoetin alfa** and Chugai-Upjohn's product **Epoetin** beta, notwithstanding the fact that, by April 1990, FDA had not officially given the designation of **Epoetin** beta to a specific manufacturer's product.

The FDA generally relies on **USAN** to adopt names for new chemical entities and biological products. **USAN** is a private organization sponsored by the USP, American Medical Association, and American Pharmaceutical Association and has been engaged in the assignment of names to drugs since January 1964. According to regulations, however, FDA retains the right to publish official names of drugs in situations in which the **USAN** or other official common name is unduly complex or is not useful for another reason, or two or more official names have been applied to a single drug, or to two or more drugs that are identical in chemical structure or pharmacological action and that are substantially identical in strength, quality, or purity (21 CFR **299c).** It appears, therefore, that FDA will make the final determinations of names for recombinant erythropoietin products.

10 **Amgen's** patent is No. 4,703,008, "DNA Sequencing Encoding erythropoietin." U.S. Patent Office Application No. 675,298.

11 Genetics Institute's Patent is No. 4,677,195, "Homogeneous erythropoietin." U.S. Patent Office Application No. 690,8S3.

other manufacturer's patent. Genetics Institute, which was producing recombinant erythropoietin in the United States for sale in Europe, was infringing on Amgen's patent, and Amgen, which was producing recombinant erythropoietin for sale in the United States, was infringing on Genetics Institute's patent. Because Chugai was producing recombinant erythropoietin in Japan, however, it was not infringing on Amgen's recombinant erythropoietin patent. According to the court, U.S. patent protection for Amgen's intermediate product does not extend to production of recombinant erythropoietin by another manufacturer in a foreign country. If Amgen had a patent on the process by which it produced recombinant erythropoietin, or a patent on recombinant erythropoietin itself, then the court might have ruled differently.

The issue of whether U.S. patent protection on intermediate products extends to production outside the United States had been raised in another dispute between Amgen and Chugai. In January 1988, Amgen asked the U.S. International Trade Commission (ITC) to block Chugai Pharmaceutical from importing recombinant erythropoietin from Japan on the grounds that Chugai Pharmaceutical was infringing Amgen's U.S. patent. Chugai Pharmaceutical was making recombinant erythropoietin by a process similar to Amgen's and importing it from its Japanese production facilities for use in U.S. clinical trials (165).

In January 1989, the ITC held that its jurisdiction did not cover the use of a patented product abroad (165). Although Chugai Pharmaceuticals indeed utilized a process similar to Amgen's in the production of Chugai's product, Amgen had a patent on one ingredient that was essential to making recombinant erythropoietin, not on the process by which it was produced. Therefore, Chugai Pharmaceutical could sell recombinant erythropoietin in the United States once it had an approved PLA and ELA for its facility in Japan from FDA, even if Chugai Pharmaceutical was making the product by a process that used Amgen's patented host cells. If Chugai produced recombinant erythropoietin in Japan by a process that Amgen patented in the United States and attempted to market it here, however, it would indeed constitute patent infringement.

Some analysts have speculated that a cross-licensing agreement between the two manufacturers will result from this decision (136). Cross-licensing is the exchange of licenses by two or more patent holders in order that each may use or benefit from the patents of the other (14). Cross-licensing could enable both Amgen to remain on the market and Chugai-Upjohn to enter and remain on the market.

On March 14, 1990, a Federal court judge in Boston ordered Amgen and Genetics Institute to submit to the court a royalty-free cross-licensing agreement with 60 days. The judge indicated that he would issue an injunction to prevent the manufacturer who was noncompliant with his order from making and selling recombinant erythropoietin in the United States (168). The judge indicated that the orphan product status of the manufacturers' products should also be resolved in the agreement (7).

These circumstances surrounding the issuance of two patents on recombinant erythropoietin products are examples of the evolving nature of this body of law. It appears, however, that the granting of two patents will result in multiple sources of recombinant erythropoietin.

RECOMBINANT *erythropoietin* AND THE ORPHAN DRUG ACT

The Orphan Drug Act of 1983 (Public Law 97-414) provides economic incentives for pharmaceutical manufacturers (sponsors) to research, develop, and market products for rare conditions. The term rare disease or condition was defined in a 1984 amendment to the Act (Public Law 98-551) as any disease or condition that 1) affects fewer than 200,000 persons in the United States or 2) affects more than 200,000 persons in the United States and for which no reasonable expectation exists that the cost of developing and making available in the United States a drug for such a disease or condition will be recovered from sales.

FDA's awarding of orphan status to a particular sponsor's product is made independently of FDA's approving the product. Before it submits a PLA to the FDA, a sponsor must apply for orphan product status to the Office of Orphan Products Development (69). Several sponsors may obtain orphan

product status for the use of a particular product for a particular condition; however, only that sponsor that receives FDA approval first receives 7 years of marketing exclusivity for that product for that condition. Although regulations to implement the Orphan Drug Act have yet to be put in final form, the Office of Orphan Products Development has been operating within the following guidelines in granting orphan product designations.

Several pharmaceutical manufacturers may obtain orphan product designations for a product's use for a particular condition. Only the sponsor whose product FDA approves for marketing first, however, is awarded the 7-year market exclusivity for that product for the approved use. FDA may grant market exclusivity to two versions of the same product if each applies for a different rare condition. In addition, FDA may grant market exclusivity to two products for the same condition, if FDA considers them different products (69).

For the purpose of orphan product designation, a sponsor makes the estimate of the patient population at the time of submission of the application, and the Office of Orphan Products Development reviews the sponsor's estimate. The Act does not currently permit FDA to remove an orphan product designation if the patient population subsequently exceeds *200,000.* Marketing exclusivity may be removed, however, if the manufacturer falsified claims in making application for the designation or is unable to produce sufficient quantities of the product for the patient population.

Amgen, Ortho, and Chugai all have orphan drug designations for the use of recombinant erythropoietin in various medical conditions (see table 3-3). Since Amgen's recombinant erythropoietin was the first to be approved by FDA, it was designated Epoetin alfa and has market exclusivity for chronic renal failure.[12]

Ortho's product has received orphan designation for anemia associated with ESRD, HIV, and infant prematurity, and Chugai's has received orphan designation for anemia associated with ESRD. Regardless of FDA's decision about whether other companies' products are different from Amgen's, if Ortho's Eprex obtains FDA approval for anemia associated with HIV or infant prematurity, Ortho could receive 7 years of marketing exclusivity for the

IL **Amgen's** original orphan product designation was for anemia associated with **ESRD.** After FDA approved **Epoetin alfa** for the broader indication of chronic renal failure, the orphan product designation and market exclusivity were expanded to reflect this broadened indication (142).

Table 3-3--Recombinant erythropoietin Products with Orphan Drug Designations, March 1990

Orphan condition	Sponsor holding designation	PLA and ELA filed	Status
Anemia of ESRD	Amgen (Epogen, Epoetin alfa)'	11/87	approved, 6/89
	Ortho (Eprex)	2/89	pending
	Chugai Pharmaceutical (Marogen)	9/88	pending
	McDonnell-Douglas		suspended
	Organon-Teknika		suspended
Anemia of HIV	Ortho (Eprex)	2/89	pending
Anemia of infant prematurity	Ortho (Eprex)		clinical trials

a Amgen's orphan product designation is for use of recombinant erythropoietin for anemia associated with chronic renal failure (142).

KEY: ELA = establishment licensing application; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; PLA = product licensing application.

SOURCES: Turner, 1990 (142); US DHHS, FDA, 1989 (161); 54 CFR 16295, April 21, 1989.

approved indication, because the same product may have orphan status for different rare conditions. By April 1990, FDA had not determined whether Chugai's or Ortho's product is different from Amgen's. If FDA finds either product structurally different from Amgen's, that company's product could theoretically be granted 7 years' exclusivity for anemia associated with ESRD or chronic renal failure. FDA had not decided by April 1990 whether the broader indication of chronic renal failure rather than ESRD would be granted to Ortho's or Chugai's product, if either was deemed different from Amgen's, was given FDA approval for the same indication, and was granted market exclusivity (142). Thus, independently of the resolution of legal disputes among the companies, FDA's decisions regarding product differentiation and market exclusivity have the potential to affect the number of companies in the U.S. market and the indications for which they may market recombinant erythropoietin.

THE SUPPLY SIDE OF THE MARKET FOR RECOMBINANT erythropoietin

Since the FDA approved Epogen in June 1989, Amgen has been the sole supplier of recombinant erythropoietin for the U.S. market. Although Amgen has held a monopoly on the U.S. sale of this biologic, certain factors have limited its market power. In the short term, Amgen has faced the Medicare program as the dominant payer of recombinant erythropoietin. Not only does Medicare command substantial leverage because of its coverage of dialysis patients, but also Amgen has been particularly dependent on Medicare revenue because Epogen is the company's first and so far its only product on the market.

The dynamics of this market also promise to limit Amgen's influence. Given developments in the legal and regulatory arenas, it is possible that in the near future, the United States will have two additional sources of recombinant erythropoietin: Ortho's Eprex and Chugai-Upjohn's Marogen. This situation illustrates several possible sources besides clinical significance from which products may draw market power: patents, exclusivity as an orphan product, agreements to divide the market among competitors, FDA approval for certain medical indications, and other differentiation from competing products.

The very purpose of a patent is to encourage innovation by granting new products a period free from competition. For products developed through biotechnology, this period of patent-protected monopoly power appears to be shorter than for other products. In the case of recombinant erythropoietin, Amgen and Genetics Institute have been challenging each other's patents. Unable to resolve the dispute through negotiation, the parties face a court order to reach an agreement to cross-license their rights without payment of royalties. Although attention has focussed on U.S. patents, the scope is properly international, with patents in Japan and Europe relevant to the overall package.

The court order also charges the companies to address another source of market power, FDA's grant of 7 years' exclusivity to an orphan product. Similar to patents, this period of market exclusivity was intended to protect orphan products from competitors and thereby to stimulate the development and testing of products for rare medical conditions. Controversy surrounds the appropriate scope of the condition considered rare and the estimate of the population afflicted. Thus, Chugai disputes the validity of the exclusivity granted to Amgen's Epogen, and Amgen opposes FDA's granting Chugai's Marogen exclusivity. Even more basic is the advisability of granting exclusivity to a product that two or more companies are developing for the same condition. In the case of human growth hormone, FDA's grant of exclusivity to more than one company, on the grounds that different structures rendered the products different entities, has allowed competitors to enter the market (10).

Both Amgen and Genetics Institute have used licensing agreements with other firms to segment the market, both domestic and international. These agreements may divide the market by medical indication, such as Amgen's retaining rights to the U.S. dialysis market and licensing rights to the predialysis population to Ortho. Or companies may

divide the market geographically, such as Genetics Institute's licensing of Boehringer-Mannheim for the European market. Especially agreements pertaining to different medical indications may prove difficult to enforce. As described below, physicians may prescribe different brands interchangeably.

FDA approval of a product for certain conditions offers another related route to gain market power. FDA approval allows a manufacturer to segment the market, since a company may promote its product only for approved indications. Ortho's Eprex has applied for approval for anemia associated with HIV and with chronic renal failure.

Like the other bases of market power, this one is also subject to encroachment. Chugai, for example, has applied for approval for anemia associated with end-stage renal disease, a medical condition that is a subset of Amgen's approved indication, anemia of chronic renal failure. Perhaps even more telling, the indications for which FDA approves different brands of recombinant erythropoietin are unlikely to restrict their clinical uses. Although FDA approves a product only for a specific indication, physicians and other providers may use it for a different indication, especially if there are economic incentives and it is clinically efficacious to do so. For example, even if Eprex becomes the only brand approved for anemia associated with HIV, physicians may prescribe Epogen or Marogen for the condition. Similarly, it may become common practice for physicians to use recombinant erythropoietin to increase autologous blood donations or to treat anemia associated with cancer therapy even before FDA approves these indications. To the extent that physicians do not restrict their use of a particular brand of recombinant erythropoietin to the indication for which it was approved, any market power that brand may have derived from FDA approval for a specific indication will be eroded.

A product may also gain market power through other methods of differentiating itself from competitors, such as by physical characteristics or through brand loyalty. By catering to the needs of different users, manufacturers attempt to segment the market and thus support higher prices and gain greater revenue. This is an effective strategy for increasing profits only to the extent that it outweighs the advantages of serving a larger share of the market. Manufacturers of recombinant erythropoietin are already adding features to differentiate their products, such as Marogen's use of a powder in contrast to the liquid form of Epogen and Eprex. Manufacturers may vary the volumes of the product's containers; some buyers may prefer large containers and others small.

Promotional activities may seek to gain a larger market share and users' commitment to a certain brand. As the first brand on the market, Epogen may acquire brand loyalty independent of Amgen's promotional activities. Brand loyalty, however, can be eroded with price concessions and other benefits offered by competing brands.

DISTRIBUTION OF RECOMBINANT erythropoietin

Recombinant erythropoietin is currently provided to patients in dialysis facilities (hospital-based or free-standing) and physicians' offices. If FDA-approved indications increase beyond chronic renal disease and if legislation is enacted to allow Medicare coverage for self-administration of this biologic, then pharmacies and dialysis distributors (when serving home dialysis patients) may also become providers. Providers share the common functions of administering or dispensing recombinant erythropoietin to patients and submitting claims to Medicare carriers or fiscal intermediaries, but only physicians and dialysis facilities make decisions about use.

Although manufacturers, wholesalers, and other intermediate suppliers may distribute recombinant erythropoietin to providers, Amgen has been selling only to wholesalers, not directly to providers. Intermediate suppliers include wholesalers, dialysis distributors (when serving dialysis facilities), pharmacies (when serving physicians), and other suppliers to physicians. Dialysis distributors specialize in equipment and other supplies relating to dialysis. Physician suppliers also deal in a wide range of products. Unlike providers, manufacturers and intermediate suppliers do not deal directly with patients and are not responsible for billing Medicare. Although

the unit cost of recombinant erythropoietin to each provider is equal to the sum of the manufacturer's price and the intermediate supplier's markup, the manufacturer's price is by far the larger component.

Chains of dialysis facilities maybe large enough purchasers to bypass intermediate suppliers and obtain a product such as recombinant erythropoietin directly from the manufacturer. smaller organizations are by far more likely to purchase products through wholesalers or dialysis distributors. Hospital pharmacies, which often jointly purchase through a buying group that deals with pharmaceutical wholesalers or directly with manufacturers, usually supply hospital-based dialysis facilities. Physician providers often obtain products from physician suppliers or pharmacies. Independent pharmacies would be likely to obtain a product such as recombinant erythropoietin from wholesalers, whereas large chains might purchase it directly from the manufacturer. Dialysis distributors would obtain the product either from manufacturers or pharmaceutical wholesalers.

Medicare beneficiaries now receive recombinant erythropoietin primarily from dialysis facilities and also from physicians' offices. If legislation is enacted enabling Medicare to cover the self-administration of recombinant erythropoietin, many home dialysis patients may choose that alternative. Home dialysis patients could obtain recombinant erythropoietin from dialysis facilities, dialysis distributors, or, if new arrangements were made, from physicians' offices or pharmacies (see ch. 4 for current policies). If self-administration was covered, Medicare beneficiaries in the predialysis phase of chronic renal failure or with future medical conditions that might be approved could also obtain recombinant erythropoietin from physicians' offices or from pharmacies.

THE DEMAND SIDE OF THE MARKET FOR RECOMBINANT erythropoietin

At present, Medicare is by far the dominant payer for recombinant erythropoietin therapy. If FDA grants approval for indications besides anemia associated with chronic renal failure, Medicare's leverage in the market will probably diminish, as other payers become more prominent. In addition to Medicare, other Federal Government programs or agencies, such as Medicaid and the Departments of Veterans Affairs and Defense, also purchase or pay for recombinant erythropoietin. If Medicare acted in concert with these other Federal programs or agencies, its market leverage would be reinforced.

Estimates of the patient populations that might use recombinant erythropoietin range widely. According to most estimates of current patients, dialysis patients who are anemic comprise the largest group, with estimates from about 59,000 in 1984 to about 92,000 in 1990 (see table 3-4) (69,103,156).

The great variation in estimates of anemic patients in the predialysis phase of chronic renal failure reflects uncertainty about the number in the predialysis phase and about the proportion who are anemic.[13] Estimates of people in the predialysis phase range from 71,000-110,000 (174) to 93,000 (164), to somewhat over 230,000 (68), to over 2 million (41). Applying estimates of the percentage of people who are anemic to these figures yields, respectively, 9,000-18,600 (10-20 percent anemic) (51,164), 23,400 (10 percent) (68), 31,200-48,400 (44 percent) (174), and 740,000 (35 percent) (29) (see table 3-4).

Although information is not available to assess fully these estimates, it is likely that the estimate of the predialysis population, made by the Degge Group, Ltd., for Chugai-Upjohn, is too high. For example, the numbers of individuals with different comorbidities were summed to derive an estimate of the total symptomatic predialysis population. Since individuals are likely to have more than one of these comorbidities, summing numbers for each comorbidity will overstate the total. This factor, however, does not fully explain the large difference between the Degge Group's estimate and the other estimates. For example, according to the Degge Group's study, the largest comorbidity, diabetic nephropathy, comprised an estimated 1.4 million people. If only these people are considered and if a more conservative 20 percent rather than 35 percent are assumed to be

13 As for dialysis patients, not all predialysis patients who are anemic may be candidates for recombinant erythropoietin therapy (see ch. 2).

Table 3-4-Estimates of Individuals With Selected Conditions Who Are Anemic

Condition	Range of Estimates		
	Low	Medium	High
Dialysis Patients	58,900[a]		92,000[b]
Predialysis Chronic Renal Failure	9,000-18,600[c]	23,400[d] 31,200-48,400[e]	740,000[f]
AIDS	17,000[g]		

[a]Based on a 1984 estimate of dialysis patients submitted by Amgen to FDA (69) and an estimate that 75 percent of them are anemic, which was calculated from 1989 hematocrit level distributions obtained from National Medical Care, Inc. (103).
[b]An estimate of the total dialysis population was derived by projecting Medicare dialysis patients, who constitute about 93 percent of the total, to 1990 (46) and adding the remaining 7 percent, who are non-Medicare patients (156). The estimate othat 75 percent of the total are anemic was based on 1989 hematocrit distributions from National Medical Care, Inc. (103).
[c]Estimate of predialysis population from the National Center for Health Statistics (NCHS) (164) and estimate of 10-20 percent of predialysis population as anemic by Eschbach (51). The NCHS figure, 93,000, was based on 1983 discharges from short-stay nonfederal hospitals for whom chronic renal failure, ICD-9-CM Code 585, was listed as a diagnosis. It should be noted that an individual with chronic renal failure may have multiple hospitalizations in a given year, and individuals with this condition who were not hospitalized were excluded.
[d]Estimate of about 230,000 predialysis patients of whom 10 percent were estimated to be anemic (68).
[e]Based on estimates from a survey of randomly selected nephrologists before recombinant erythropoietin was approved: 71,000-110,000 predialysis patients of whom 44 percent had symptomatic anemia. Of these 44 percent, respondents thought 40 percent would be candidates for the biologic (174).
[f]Based on an estimate of over 2 million individuals with symptomatic chronic renal failure who are predialysis (41) and an estimate that 35 percent are anemic (132). The number of individuals with symptomatic chronic renal failure was based on prevalence estimates for this condition among the several comorbidities with which it is commonly associated. The percent anemic was based on an estimate of those with the condition who have a blood hemoglobin less than 10 g/all or hematocrit less than 30.
[g]calculated from an estimate of people living with AIDS in January 1990 (158) and the percent of these likely to become anemic subsequent to zidovudine use (119).

SOURCE: Office of Technology Assessment, 1990.

Table 3-5-Projections of Medicare-Eligible Dialysis Patients Who Are Candidates for Treatment With Recombinant erythropoietin by Age Group, 1990-1995[a]

Age group	1990	1991	1992	1993	1994	1995
0-14	607	605	600	593	583	572
15-24	3,021	3,135	3,224	3,291	3,335	3,357
2.5-34	7,385	7,401	7,347	7,230	7,059	6,837
3544	11,126	11,786	12,434	13,059	13,652	14,203
45-54	13,470	14,624	15,867	17,180	18841	19,932
55-64	19,421	20,715	22,100	23,543	25,011	26,476
65-74	19,717	20,927	22,232	23,588	24,957	26,303
> 75	10,789	11,860	13,052	14,333	15,673	17,042
TOTAL	85,536	91,053	%,856	102,817	108,811	114,722

[a]Based on current treatment guidelines to use recombinant erythropoietin for a hematocrit of less than 30 percent.

SOURCE: Office of Technology Assessment, 1990. Based on data obtained from Eggers, 1989 (46) and National Medical Care, 1989 (103).

anemic, the estimate would still be relatively high, 280,000. There is some question, however, about the number of people with diabetic nephropathy who have symptomatic chronic renal failure. Although the Degge Group assumed that, overall, 22 percent of those with diabetic nephropathy have chronic renal failure, estimates cited in the literature start at 10 percent (41).

FDA is reviewing Ortho's PLA for anemia associated with HIV and, specifically for anemia associated with treatment with zidovudine. In January 1990, people living with acquired immunodeficiency syndrome (AIDS) numbered about 50,000 (158). Compared with untreated AIDS patients, about 34 percent more AIDS patients treated with zidovudine at 1,500 mg daily experienced a 25-percent or greater decline in hemoglobin levels from an initial level of 9.5 g/all or higher (119). About 17,000 people with AIDS could thus be candidates for recombinant erythropoietin. Although this figure is probably an underestimate of people infected with HIV who would be candidates for recombinant erythropoietin, it is difficult to estimate this population as well. About 12 percent of people with AIDS-related complex had similar declines in hemoglobin levels from zidovudine treatment. FDA has recently approved zidovudine for infected people with CD4-cell counts below 500, even if they are asymptomatic (163). But people earlier in the progression of disease have been less likely to develop anemia from treatment. Moreover, the recommended dose of zidovudine has been greatly reduced, from 1,200 mg to 500-600 mg daily (24, 162). Over time, as the HIV epidemic progresses, the population infected with HIV and those who develop AIDS will increase, but lower doses of zidovudine may reduce the likelihood that treated patients will develop anemia and use recombinant erythropoietin. Development of an effective and safe therapy for HIV infection that does not induce anemia would also lower the potential use of recombinant erythropoietin among this population.

Although Medicare expenditures for recombinant erythropoietin will most likely continue to increase, over time Medicare's share of the U.S. market will undoubtedly decline. Besides growth in Medicare's ESRD population, Medicare's share of the market in future years depends on FDA approval of additional indications, the sizes of the additional population, the proportions of these populations that are Medicare beneficiaries, and the extent to which other third-party payers cover recombinant erythropoietin.

Only for Medicare's dialysis population were data sufficient to make projections for future years. Future estimates of Medicare dialysis patients depend on several factors: the number of patients who initiate treatment in any one year; the number of patients who have a successful kidney transplant in each year and no longer need dialysis; the number in each year who have a failed transplant and must return to dialysis; and the number of patients on dialysis who die. Using these factors, Eggers developed a model that projects the number of total ESRD, dialysis, and transplant patients to the year 2000 (46). For each projection year, a low, midline, and high estimate of each population component was provided. OTA used Eggers midline projections of the dialysis component, to the year 1995, to estimate the number of beneficiaries on dialysis who will be candidates for treatment with recombinant erythropoietin (see table 3-5).

The calculations in table 3-5 assume that all dialysis patients with a hematocrit level of less than 30 will be eligible for treatment. The proportions, by age group, of dialysis patients with hematocrits below 30 were obtained from National Medical Care (NMC), the largest chain of U.S. dialysis facilities (11). These proportions were applied to Eggers' projections to generate the estimates in table 3-5. The information from NMC pertained to the largest Medicare beneficiary and patient group for which data were available; NMC treats about 20 percent of Medicare dialysis patients and operates in over 30 States (11). There is no reason to expect that the prevalence of anemia as an underlying condition in dialysis patients will change, although use of recombinant erythropoietin during the predialysis phase may increase the average hematocrit level of patients starting dialysis.

The estimates in table **3-5** understate total Medicare beneficiaries who may be candidates for recombinant erythropoietin through 1995. These estimates include neither beneficiaries in the predialysis phase nor those with other indications that might be approved by FDA.