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Rivals Laying Siege to Amgen's Near Monopoly in Anemia Drugs

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For years, the biotechnology giant Amgen has wielded a near monopoly over its industry's most lucrative franchise, the anemia drugs on which hundreds of thousands of American kidney and cancer patients and their insurers spend billions of dollars each year. But now, Amgen's money machine is coming under attack.

A host of companies - ranging from the Swiss giant Roche to Silicon Valley start-ups - are developing anemia drugs to compete against Epogen and Aranesp, the blockbusters that will account for nearly half of Amgen's expected $12 billion in revenues this year.

But Amgen, the world's largest biotechnology company, will not give up its empire without a fight. Last month it filed a pre-emptive patent infringement suit against Roche, setting the stage for what Mark Schoenebaum, biotechnology analyst at Bear Stearns, predicts will be "the mother of all biotech patent cases." He estimated that Amgen's annual earnings growth over the next five years could be cut by more than 50 percent if Roche were to capture half the American market.

While a potential blow to Amgen and its shareholders, competition would be good news for consumers, insurers and taxpayers. Collectively, they will spend about $7 billion this year for Epogen and Aranesp and for the Johnson & Johnson drug Procrit, which is sold under license from Amgen. Medicare spends more on those drugs than almost any other, laying out at least $1 billion a year for each.

Some Amgen critics say that while its anemia drugs have truly helped people, its near monopoly is lasting much longer than patent law was meant to allow. The company has sold about $22 billion worth of Epogen since its approval in 1989 and $7 billion worth of Aranesp, a newer, longer-lasting version, since 2001.

"Simply put, this is a monopoly within Medicare that is now working against the patients it was intended to help and is costing U.S. taxpayers billions of dollars," Gary Peterson, the president of Renalweb, a Web site about dialysis, wrote in July after a price increase for Epogen.

Epogen, used by most of the nation's 300,000 dialysis patients, costs about $7,000 to $10,000 a year. Aranesp and Procrit, which do compete against each other, are used primarily to treat the anemia caused by cancer chemotherapy and cost $1,200 or more a month. Amgen gets a 10 percent royalty on Procrit sales in the United States.

In Europe, Amgen's original patent on the drugs has expired and competition is set to begin. Roche plans to introduce its drug CERA, which it claims is better than Amgen's products, in 2007. Several companies are planning lower-priced generic versions of Epogen.

In the United States, Amgen received seven patents. All were based on the work done in the early 1980's by one of its scientists, Fu-Kuen Lin, who isolated the human gene for erythropoietin, or EPO, the protein that makes up the drugs.

While the first of these patents expired late last year, the others were not granted until the mid-to-late 1990's and could preserve Amgen's monopoly until 2015 - well beyond the 17 or 20 years contemplated in patent law for an innovation.

"Amgen is absolutely determined to ensure that this is the case, that the effective patent life for EPO in the United States will be 32 years," said C. Boyd Clarke, the chief executive of Neose Technologies, which is trying to develop EPO in a way that would get around Amgen's patents.

Even Kevin W. Sharer, Amgen's chief executive, when asked why EPO's patent life lasted so long, replied, "It's an obvious question; I've had it myself."

He and other Amgen executives say that the patent office delayed issuing the patents in part because of years of challenges from Amgen's competitors.

"Because we lacked protection for many of our inventions, we pushed hard to get those patents issued as soon as possible," Stuart Watt, Amgen's chief patent counsel, said in a written statement.

But critics note that Amgen played a role in the protracted process. Some of its applications were repeatedly rejected or abandoned and then resubmitted with different wording, keeping the patent application mill grinding for years.

All of the patents contain an identical description of the work done by Mr. Lin. But each contains different claims. The original, for instance, covered the EPO gene. Others deal with genetically engineered cells for making EPO; with processes for manufacturing; with drugs using the protein; and with methods of treatment.

Experts say Amgen's approach was common until the mid-1990's. In some cases examiners requested that a patent be divided.

"That's not an abuse of the system; that's the way it was done," said Rochelle Seide, a biotechnology patent lawyer with Arent Fox in New York who is not involved in litigation involving EPO. She said Amgen's patents "have been examined and re-examined" and have held up.

American patent law was changed in 1995 to prevent such extensions of patent life. Under the new law, protection lasts for 20 years from the date of application, not 17 years from the date a patent is issued. But because Amgen filed new applications for several of its patents just before the new law took effect, they fell under the old law.

Amgen did not invent EPO, a natural protein made by the kidneys that increases the production of oxygen-carrying red blood cells. Scientists had surmised EPO's existence since the early 1900's, and tiny amounts were first purified from human urine at the University of Chicago in 1977, three years before Amgen was founded. The Chicago researcher, Eugene Goldwasser, even treated three anemic patients but had too little of the substance to show a meaningful improvement.

Mr. Goldwasser gave some of his precious material to Amgen, which allowed Mr. Lin to find the gene. The human EPO gene was then spliced into hamster cells, allowing cultures of those cells to

produce EPO in large enough quantities to use as a drug. Millions of anemic people have since benefited from having greater energy and avoiding the risks of repeated blood transfusions.

In a race to find the EPO gene, Mr. Lin beat a team from a company called Genetics Institute by only a few weeks. But in patents, the winner takes all. Amgen also won litigation against Transkaryotic Therapies, a Cambridge, Mass., biotechnology company that produced EPO by activating the dormant EPO gene in cultures of human cells, rather than splicing that gene into hamster cells. TKT argued that Amgen had improperly broadened the claims in its later applications to cover what TKT had done. One Amgen patent covers any therapeutic EPO produced in mammalian cells, which would include human cells.

In 2001, Judge William Young of Federal District Court in Boston ruled that Transkaryotic, generally known as TKT, had infringed on Amgen's patent. That ruling is being appealed.

In Europe, however, TKT prevailed. Shire Pharmaceuticals, which acquired TKT for $1.6 billion this year, has said it will begin selling the drug Dynepo in Europe in the first half of 2006.

Amgen's next challenge will come from Roche, which already sells a version of EPO, called NeoRecormon, in Europe based on patents obtained there by Genetics Institute.

Roche says its new drug CERA can be injected as infrequently as once every four weeks, compared with as often as three times a week for Epogen and Procrit. Aranesp is used once every week or two weeks in the United States, but Amgen hopes to win approval for use every four weeks, as it has done in Europe.

Roche said it would file for approval in the United States and Europe in 2006, meaning the drug could reach the market in 2007. Amgen filed its suit against Roche in Boston and, as it apparently wished, the case was assigned to Judge Young, who ruled in the company's favor against Genetics Institute and TKT. No court dates have been set yet.

Roche has said it is confident CERA does not infringe and has been granted its own American patent. "It is novel," said Philippe Van der Auwera, business director for Roche's anemia franchise, adding that the drug acts differently in the body. There is still some mystery as to what CERA is. It is EPO linked to a chemical that makes it last longer in the bloodstream. Roche might try to make part of the protein chemically so that it would not infringe on Amgen's patents for manufacturing EPO in mammalian cells.

If Amgen cannot win or get an injunction, Roche could begin selling CERA after getting approval from the Food and Drug Administration - at the risk of having to make stiff payments to Amgen if it is later found to have infringed.

While a brand-name drug like CERA would pose new competition to Amgen, it might not have much impact on overall prices. Generic versions of EPO could bring price pressure, though, and some of these are expected to go on the market in Europe over the next two years. So far, EPO generics are being kept out of the American market not only by Amgen's patents but by a lack of regulations for approving copies of biotechnology drugs.

Other companies hope to get around Amgen's patents entirely.

The most closely watched is FibroGen, a privately held company in South San Francisco. Its drug,

which is not EPO, activates the body's mechanism for coping with low oxygen levels like those that occur at high altitudes, when the body responds by making more EPO.

And FibroGen's drug is a pill rather than an injected protein, making it potentially more convenient for patients than EPO and also far less costly. The drug has shown signs of effectiveness in early clinical trials, but is not expected to reach the market before 2009. And there are some theoretical safety concerns. (Amgen at one time discussed buying FibroGen or licensing its drug, according to executives at both companies.)

Another privately held company, Affymax of Palo Alto, Calif., is in midstage testing of a small protein that mimics EPO but is not similar to it structurally.

Two other companies, meanwhile, are trying to get around Amgen's patent on making EPO in mammalian cells. Neose of Horsham, Pa., is trying insect cells. GlycoFi, based in Lebanon, N.H., has produced EPO in yeast.

Another company, DNAPrint Genomics, has rights to a discovery by Arthur Sytkowski of Beth Israel Deaconess Medical Center in Boston, who found that two linked EPO molecules are more powerful than a single one.

"Those of us in medical areas try to make improvements on things so that medicine advances," said Dr. Sytkowski, who has been doing research on EPO for 30 years and was an expert witness in an unsuccessful challenge of Amgen's patent in Europe. "That's why a patent is a limited monopoly, limited in time and limited in scope."