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Lucrative Niches

How Drugs for Rare Diseases Became Lifeline for Companies

Federal Law Gives Monopoly For Seven Years, Fueling Surge in Biotech Profits A Teen's \$360,000 Treatment

By GEETA ANAND

When an experimental medicine helping her son was dropped because it didn't seem profitable, Connecticut homemaker Abbey Meyers turned into a lobbyist. Her crusade: Change the law to create incentives to develop drugs for rare diseases.

Congress responded with the Orphan Drug Act of 1983, giving companies a seven-year monopoly for bringing a new treatment for a rare disease to market. Within two years, a drug was approved to treat Tourette's syndrome, the disease Ms. Meyers's son has. At the time, Margaret Heckler, then health and human services secretary, predicted orphan drugs "will make nobody rich, but they will help treat a small group of tragically handicapped people."

It didn't turn out quite that way.

Drugs for "orphan" diseases (so-called because no one was treating them) have benefited many people with rare illnesses. But what was originally envisioned as a modest sideline for drug

companies has instead become a multibillion-dollar business. With no cap on prices and patients with few options, companies found they could profit in small markets—charging as much as \$600,000 a year per patient for drugs that people would need their entire lives.

There are 260 orphan drugs now on the market and 1,400 under development. Some orphan drugs have revenue of more than \$1 billion a year, the industry's measure of a blockbuster.

Orphan-drug status is granted by the U.S. Food and Drug Administration. For seven years, it gives a company, in effect, the same market protection that a patent does, without requiring the company to go through the lengthy process of getting a patent. (A patent for a scientific discovery is good for 20 years from filing, but typically there are about 10 years remaining on it by the time it results in an approved drug.) Unlike a patent, which is granted for a new discovery, orphan-drug status can be given to a drug that has been on the market in the U.S. for other diseases or used in other countries for years.

While companies often have to battle competing patent claims in court, orphan drugs are protected by the FDA, which is barred by law from approving another drug with the same active ingredient unless it is proven clinically superior for that disease.

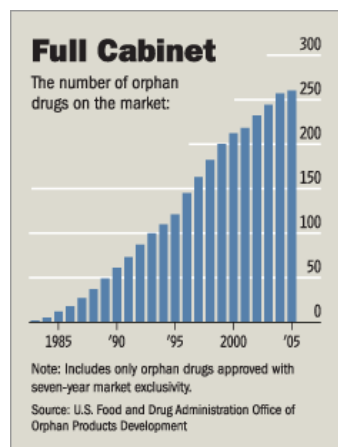
"It's much more valuable than a patent for that period of time," says

Sherrill Neff, a managing partner at Quaker BioVentures Inc., a Pennsylvania biotech venture-capital firm. The law also granted companies a 50% tax credit for research and development, grant money to defray the cost of testing, and assistance in getting products approved.

The law gave a powerful boost to the biotechnology industry, which was in its early days when the act was passed. Today, nearly half of all drugs produced by biotech companies are for orphan diseases. Two of the biggest biotech companies in the world, Amgen Inc. and Genentech Inc., were built on orphan drugs. Companies have secured millions in funding and gone public based on the prospect of an orphan drug.

Even very small markets have proved profitable. Last year, Genzyme Corp., a Cambridge, Mass., biotech firm, posted sales of \$840 million on its drug for Gaucher disease, which affects fewer than 10,000 people world-wide. Treating the average patient costs \$200,000 annually, the company says. But the price of the drug, dosed by weight, can run as high as \$600,000 a year for adults on the higher of two recommended doses. Although the monopoly period for the drug has run out, like many biotech drugs it remains free of competition, in part because federal regulations don't allow generic-drug makers to easily sell copies.

The cost of such drugs has grown so dramatically that employers and



insurers are now pushing back. Some health plans are excluding coverage of certain orphan drugs. Others are requiring employees to pay as much as half of the cost of the pricey medicines. All this makes it tougher for patients to get the very drugs that the Orphan Drug Act helped make possible.

“We have all of these new fantastic new drugs, but nobody—not employers, not employees—can pay for them,” says Ms. Meyers, who now heads the National Organization for Rare Diseases, a nonprofit advocacy group. (Her son, now 37, is doing well on a medicine that isn’t an orphan drug.)

Ms. Meyers hadn’t envisioned such turmoil would arise from her efforts to get a medicine for her son’s Tourette’s syndrome, a disease that causes involuntary muscle movements and sounds. An estimated 100,000 people in the U.S. have Tourette’s syndrome. McNeil Laboratories, a division of Johnson & Johnson, was developing a drug that looked promising for Tourette’s. But the company discontinued development of the drug after it failed in tests for treating another, more common disease.

Ms. Meyers helped build a coalition of patients that urged Rep. Henry Waxman, a California Democrat, to pursue legislation pushing the drug industry to develop medicines for rare conditions. Ms. Meyers argued her case through the prism of civil rights: People with rare diseases were being discriminated against because of their small numbers.

Testimony by ‘Quincy’

Her crusade gained steam when actor Jack Klugman, whose brother had a rare bone cancer, made an episode of the television series “Quincy,” in which a patient couldn’t get a treatment because no company

found it profitable enough to market. In crowded congressional hearings in 1981, Mr. Klugman testified in support of patients.

Those initially involved with the law didn’t think these niche drugs would be a profit center. “All we wanted to do was make products available for patients who had these rare diseases,” says Marion Finkel, former head of the FDA’s Office of New Drug Evaluation. A report she wrote in 1979, recommending incentives for such treatments, called them “Significant Drugs of Limited Commercial Value.” She says: “We were thinking of chemicals that are relatively inexpensive.”

When President Reagan signed the Orphan Drug Act in 1983, the biotechnology industry was in its infancy. Unlike traditional medicines, which are made by mixing chemicals, biotechnology drugs are typically proteins produced by live cells, grown in sterile, temperature-controlled containers. The complexity of the process of coaxing the cells to make biological matter makes them more expensive to produce.

“We did not expect to see the high cost of orphan drugs,” Rep. Waxman says today. While the seven-year monopoly guaranteed by the legislation “is obviously quite effective at generating interest in certain drugs by pharmaceutical companies, it also has the unfortunate consequence of increasing prices.” He says the price of drugs “is unfair across the board, and Americans everywhere are getting fed up.”

Drug company executives say they need to make sizeable profits so they can invest in research and development of new medicines. They say the high prices reflect the value of products that save lives. They note they help patients who can’t afford certain drugs by giving some of it away.

“When you have small populations,

the cost per patient is very high,” says James Greenwood, president of the Biotechnology Industry Organization, a Washington trade group. “Without our making these drugs, patients would have no alternative but to suffer and die.”

At first, most employers and insurers didn’t worry too much about the price of orphan drugs. The diseases were thought to be so rare that most insurers were likely to have few patients needing them in their health plans.

But it turned out that there are a lot of orphans. The act defines orphan diseases as those which affect fewer than 200,000 people. In 1989, a congressional commission estimated that, by that measure, one in 10 Americans suffers from an orphan disease. Many different types of cancer are classified as separate orphan diseases.

The biggest biotechnology companies got their start with orphan drugs. Genentech received orphan-drug protection in 1985 for its first drug, human growth hormone, to treat children who weren’t growing properly because of a hormone deficiency—a population of about 20,000 in the U.S. Revenue grew rapidly as the drug became more widely used. Last year, 19 years after the first version came to market, the drug yielded Genentech revenue of \$354 million.

Amgen got its first product, Epogen, approved in 1989 as an orphan drug for treating anemia in dialysis patients, a population estimated at less than 200,000 at the time. Revenue from Epogen grew quickly to \$1.4 billion by 1996 and \$2.6 billion last year. About 250,000 people are now estimated to suffer from the condition.

Even after the seven-year monopoly expires, there is often no competition for many orphan drugs. That’s because there is no federal process for gaining approval of generic versions of biotech drugs. For regular pills such as Prozac,

a generics company merely must show that its product is identical to the original in order to win FDA approval. But it's harder to prove equivalence in biotech drugs—biotech companies with big-selling products say it's impossible. A generics maker would have to spend tens of millions of dollars for full clinical trials to win FDA approval. This is usually considered too expensive.

Henry Blair had been making an experimental enzyme under government contracts while he was a researcher at Tufts University School of Medicine. The enzyme was developed by scientists at the National Institutes of Health as a treatment for Gaucher disease, a rare, sometimes fatal, condition that causes certain organs to swell and bones to deteriorate.

In 1981, when Mr. Blair co-founded Genzyme, the government transferred the contract to make the enzyme to his new company. At first, the experimental treatment didn't seem to have much commercial potential because of the small market. Before the Orphan Drug Act, investors' "eyes would roll back in their heads when I said there were, maybe, 4,000 patients" in the U.S. with Gaucher disease, he says.

Genzyme hired Henri Termeer from a company that sold a \$50,000-a-year product for hemophiliacs. Mr. Termeer envisioned an even higher price for the Gaucher drug. "I never dreamed we could charge that much," says Mr. Blair, who remains on Genzyme's board and is chief executive of another biotech firm developing an orphan drug.

In 1991, Genzyme brought the treatment to market, charging an average price of \$200,000 a year per patient.

Enzyme From 22,000 Placentas

Genzyme explained the price by not-

ing how difficult it was to produce: Originally, it took enzyme from 22,000 human placentas to make enough medicine to treat one adult patient each year. The company also gave the drug free to certain patients.

Still, the cost was so high that in 1992, the federal Office of Technology Assessment, conducted an investigation into the development of the drug. The report estimated Genzyme spent \$29.4 million to develop the drug. It said much of the initial research was done by scientists at the NIH and paid for by the government.

The report said the company loses money on each unit given free but makes far more by charging insurers the full price. Genzyme may have experienced more "resistance to the pricing among patient advocates" if it weren't for the free drug program, the report said. No major legislative change resulted after the report, and the cost of the drug remained the same.

In 1994, Genzyme figured out a cheaper and safer way of producing the drug, growing the enzyme in genetically modified cells. The Orphan Drug Act entitled the company to another seven-year market exclusivity for the new version. Today, after 14 years on the market, the Gaucher drug remains at an average price of \$200,000 per patient each year.

Mr. Termeer, Genzyme's chief executive, says that given inflation, "the price is somewhat lower today." He says economies of scale have reduced the cost of making the Gaucher drug, but he declines to say what the production cost is today.

Asked why the company hasn't lowered the price, he says, "What's the difference between charging \$200,000 or charging \$175,000 to a patient? No one can afford it without insurance. We prefer to give it away for free if people can't afford it." About 10% of the people now taking the drug get it at no cost, he says.

Propelled by revenue from the

Gaucher medicine, Genzyme has bought other companies and today develops and sells medicines for cancer, cardiology and kidney disease, as well as orthopedics and diagnostics. Still, the orphan drug for Gaucher remains by far the company's biggest source of profit. About one-third of the company's \$2.2 billion in revenue last year came from the drug.

Like other medicines, there is no limit on what companies can charge for orphan drugs. "We live in a free economy," says Marlene Haffner, director of the Office of Orphan Products Development at the FDA. That office reviews applications and decides which products receive orphan drug status. "I don't want companies to gouge patients, but I also want to see good innovation and excitement in the health-care arena," she says.

When companies profit on orphan drugs, it spurs interest in the field, she says. Yet when it comes to Genzyme's Gaucher treatment, Dr. Haffner says: "I just find it unconscionable that someone can charge that much."

Current ways of coping with exploding orphan-drug costs "are bad things—they don't accommodate well the needs of patients," says Scott Howell, vice president of pharmacy affairs at Highmark Inc., a nonprofit Blue Cross and Blue Shield insurance company in Pittsburgh. Insurers are using "blunt-instrument approaches" to manage costs such as making employees pay a big percentage of the bill, even as they scramble to develop better methods, he says.

Annual spending on specialty pharmaceuticals—the term health-insurance providers use for biotech medicines that treat smaller patient populations including orphan drugs—rose 23% per member from 2002 to 2003, according to a study funded by the Blue Cross and Blue Shield Foundation on Health Care.

To manage these costs, WellPoint

Inc., an Indianapolis-based insurer with 30 million members, and others are starting or acquiring units that specialize in controlling costs for biotechnology drugs. These companies try to bargain with biotech companies, as insurers do, to get discounts by buying in volume or buying several products. But because there isn't much competition and the markets aren't big, there's less room to negotiate discounts. "We now recognize this is an extraordinary cost," says Sam Nussbaum, chief medical officer at WellPoint.

A Savior for Brian

For patients, orphan drugs have been a savior. When their son Brian was 2 years old, Ed and Peggy DeGrenier of Lombard, Ill., learned the boy had Gaucher disease. It caused his liver and spleen to become so swollen the toddler had trouble walking and getting up when he fell.

In 1991, Brian got his first treatment with Genzyme's new medicine. Within two years, he looked and acted like any other kid. Today a high-school senior, Brian continues to receive biweekly infusions, and is so strong he swims competitively, specializing in the 100-meter butterfly.

But his father worries about how his son will fare in the future. Mr. DeGrenier says he once felt pressured to leave a job with a small employer because the cost of his son's drug

made everyone's insurance premium unaffordable. He says he realized he needed to work for a large employer so the price of the Gaucher drug could be spread among thousands of people. After searching for three years, he finally found such a job this year, selling cable services door-to-door for Comcast Corp. "At age 57, I have to get used to knocking on 60 to 70 doors a night," he said. "But I'm here for as long as Comcast will have me."

Mr. DeGrenier, who has become an outspoken critic of the drug's high price, fears it may make it hard for his son to get a job or health insurance. Brian now weighs 143 pounds and his treatment costs about \$360,000 a year. "Think of the wake this is creating," Mr. DeGrenier says. "Think of how many employers Brian is going to bankrupt."

Abbie Leibowitz, a former Aetna Inc. chief medical officer who now runs Health Advocate, a private firm advising 800 employers and their employees on health insurance, says he often hears from people who say they have been targeted for layoffs because of the high cost of their medicines. It's illegal to fire a person because of health costs, but Mr. Leibowitz says it can be hard to prove that was the reason a worker was terminated. "It's all a reflection of the fact that in the present environment, the people paying for health care can't afford to cover everything," he says.

The rising cost is especially hard on smaller companies. In 2002, Jerry Kelley, then overseeing benefits at Fruth Pharmacy Inc., a chain of 22 drug stores in West Virginia and Ohio, faced a tough choice. Staying with the company's existing health plan, which covered even the most expensive drugs, would have raised the company's health-insurance costs by 35%. "We just couldn't afford that," he says.

Mr. Kelley switched the company to a new Blue Cross and Blue

Shield plan that trimmed benefits in several ways. One of them was to make employees pay 30% of the cost of expensive medicines, including orphan drugs.

John Ash, 51, a cashier at the Fruth Pharmacy in Pomeroy, Ohio, was diagnosed with chronic myeloid leukemia in March 2003. The government defines this type of leukemia as an orphan disease. Mr. Ash's doctor prescribed one of the new orphan drugs, Gleevec.

Mr. Ash learned he would be required to pay \$771.72 of the medicine's nearly \$2,600 retail price. That would have absorbed more than his entire take-home pay for the month. He and his wife of 20 years, Diana, a dental assistant, each make about \$7 an hour. To pay for the drug, they say they emptied their savings account of \$3,000 and cashed in Ms. Ash's \$4,300 IRA.

A year and a half later, at Mr. Ash's checkup, oncologist Vinay Vermani looked at his blood report and saw his white blood cell count had soared to five times the normal level.

"Maybe the medicine is not working," Dr. Vermani says he told Mr. Ash.

"I can't afford the prescribed dose," Mr. Ash replied. "I'm taking half."

To find a way for him to afford the full dose, the doctor, his nurse, and Mr. Ash's wife began calling his employer, his insurer and the manufacturer of the drug, Novartis AG of Switzerland.

Like most drug companies, Novartis offers free medicine only to uninsured people. The company eventually directed Mr. Ash to a charity, funded in part by Novartis, that would make his monthly co-payment. One month after Mr. Ash went on the full dose, his white-blood-cell count fell into the normal range, where it has stayed ever since.

"It's terrible having this kind of technology when nobody can afford to pay for it," says the nurse, Sandy Corbin. "It bankrupts our patients."



Ralf-Finn Hestoft

Ed and Peggy DeGrenier with their 17-year-old son, Brian, whose drug for Gaucher disease costs about \$360,000 a year.

A Novartis spokeswoman says the company has a hotline to advise patients on Gleevec who need help paying for the medicine. She said Novartis couldn't discuss any particular patient's case.

Even with its employees paying higher co-pays, Fruth Pharmacy's health-insurance costs rose 15% in 2004 over the previous year. Over the past five years, the cost of insuring its employees has increased to \$1.5 million from \$600,000. "We've tried to take an analytic business approach with a heart," says Mr. Kelley, who has since retired.

Attracting Start-Up Capital

The orphan-drug market has helped companies attract start-up capital. In 1999, BioMarin Pharmaceutical Inc., a California firm, raised \$67 million in an initial public offering based mostly on the promise of a single orphan drug still in clinical trials—a potential treatment for a rare genetic disease called mucopolysaccharidosis I. Fewer than 4,000 people in the developed world are estimated to suffer from the disease, caused by a deficiency in an enzyme that leads to delayed mental development and impaired vision, among other symptoms.

Within months of going public, BioMarin had a market capitalization of more than \$1 billion.

BioMarin, in a joint venture with Genzyme, brought the treatment to market in 2003 at an average cost of \$175,000 per patient each year. The joint venture is projected to have sales of about \$70 million for the drug this year.

Orphan-drug status can also be given to older medicines, if they are being used in new ways. This has allowed companies that didn't originally pay development costs of a drug to receive protection from competition.

Celgene Corp. brought a thalidomide

pill to market at the price of \$6 a pill in 1998 and has since raised the price to about \$53. Though thalidomide has been around for decades, it received orphan-drug status for its use in treating a side effect of leprosy, then later for a certain kind of cancer.

The drug is so inexpensive to make that it is sold by other companies in Brazil for seven cents a pill.

Thalidomide was pulled off the market in the 1960s for causing birth defects. Celgene was able to persuade the FDA to approve the medicine under a tight distribution system, requiring patients to take regular pregnancy tests, among other things.

Soon after the drug came to market in 1998, doctors discovered it helped treat a rare type of cancer called multiple myeloma. The company's chief executive, John Jackson, raised the price—not because it cost more to make or market, but because, he says, many cancer drugs were priced much higher.

A new orphan drug, Velcade, came to market for the same cancer in 2003. Millennium Pharmaceuticals Inc. of Cambridge, Mass., which says it spent many years and millions of dollars developing Velcade, priced it at about \$4,400 a month. Mr. Jackson saw the price of Velcade as an opportunity to raise the price of his company's drug further. "We certainly felt that from a competitive perspective that would be justifiable," he says.

Mr. Jackson says price increases help his company develop new drugs and don't affect patients. "Either people are wealthy enough to pay or health insurance pays or our company gives the medicine available for free," he says. Celgene gives the drug free to patients without insurance, if they earn less than \$38,000 a year and have assets valued at less than \$10,000. A spokesman says

Designer Medicines, Designer Prices

ORPHAN DRUG	COMPANY	DISEASE	U.S. 2004 REVENUE	AVERAGE PRICE PER PATIENT
Rituxan	Genentech, Biogen Idec	Non-Hodgkin's lymphoma	\$1.6 billion	\$12,500 per year
Cerezyme	Genzyme	Gaucher disease	\$840 million ¹	\$200,000 per year
Gleevec	Novartis	Chronic myeloid leukemia	\$368 million	\$37,000 per year
Epogen	Amgen	Anemia from renal failure	\$2.6 billion	Unavailable ²
Avonex	Biogen Idec	Multiple sclerosis	\$922 million	\$14,000 per year
Velcade	Millennium	Multiple myeloma	\$143 million	\$22,000 for 4 months

¹Figure represents world-wide sales because company does not break out U.S. sales, which account for less than half of the total.

²Amgen and Centers for Medicare and Medicaid Services unable to provide average cost per patient annually, saying dosage varies widely.

Note: Prices are average sale prices charged by drug manufacturers, as reported to CMS. For Gleevec, the price reflects the discount CMS receives from the average wholesale price. Price paid by consumers is typically 20% to 50% higher.

Sources: Drug makers; Centers for Medicare and Medicaid Services

Celgene also donates to groups that help low-income patients with high co-payments.

The orphan-drug market has become so hot that five different companies are now vying to bring to market the first treatment for hereditary angiodema—a disease estimated to affect about 6,000 people in the U.S. "We couldn't have raised millions without the Orphan Drug Act's protection against competition," says Judson Cooper, chairman of Lev Pharmaceuticals Inc., one of the five companies.

The company was founded in 2003 with the goal of getting FDA orphan-drug approval to market a treatment that has been sold in Europe for 30 years. The disease causes sudden swelling in the hands, feet, abdomen and throat, which is painful and sometimes fatal.

Joshua Schein, Lev's chief executive officer, says he's sensitive to the wishes of a patient-advocacy group for the disease that has urged his company to price the drug close to the European price of about \$1,500 a dose or \$18,000 annually. But he says he also needs to consider the wishes of his investors. They are looking for him to price the drug close to the market price for other blood products in the U.S. that can cost well over \$100,000 a year.