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

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

...
Genzyme explained the price by noting 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 1991, 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
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.”
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 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 angioedema—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.

### Designer Medicines, Designer Prices

<table>
<thead>
<tr>
<th>ORPHAN DRUG</th>
<th>COMPANY</th>
<th>DISEASE</th>
<th>U.S. 2004 REVENUE</th>
<th>AVERAGE PRICE PER UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituxan</td>
<td>Genentech</td>
<td>B-cell leukemia</td>
<td>$36.8 billion</td>
<td>$3,500 per year</td>
</tr>
<tr>
<td>Ceretryx</td>
<td>Genzyme</td>
<td>Gaucher disease</td>
<td>$8.0 billion</td>
<td>$180,000 per year</td>
</tr>
<tr>
<td>Gleevec</td>
<td>Novartis</td>
<td>Chronic myeloid leukemia</td>
<td>$388 million</td>
<td>$57,000 per year</td>
</tr>
<tr>
<td>Sarpogrelate</td>
<td>Arixon</td>
<td>Angina from renal failure</td>
<td>$2.3 billion</td>
<td>Unavailable*</td>
</tr>
<tr>
<td>Arusole</td>
<td>Biogen Idec</td>
<td>Multiple sclerosis</td>
<td>$927 million</td>
<td>$12,000 per year</td>
</tr>
<tr>
<td>Velcade</td>
<td>Millennium</td>
<td>Multiple myeloma</td>
<td>$1.43 billion</td>
<td>$22,000 for 4 months</td>
</tr>
</tbody>
</table>

Note: Prices are average retail prices charged by drug manufacturers, as reported to CMS. For Sarpogrelate, the other reflects the discount CMS selects from the average wholesale price. Price paid by government is typically 20% to 50% higher.

Sources: Drug価格, Centers for Medicare and Medicaid Services.