CASE 24

GENZYME'S FOCUS ON ORPHAN DRUGS[1]

In 2015, Genzyme, a subsidiary of Sanofi, was one of the world's leading biotech companies. Genzyme's products and services were focused on rare, inherited disorders and diseases, and multiple sclerosis. The company was consistently recognized as a leader across many dimensions of its operations. It had been named to numerous national "best places to work" lists, and the journal *Science* had regularly named Genzyme a "Top Employer" in its annual survey of scientists.[2] The company had also won numerous awards for practicing environmental sustainability and ethical responsibility. In 2007, Genzyme received the National Medal of Technology, the highest honor awarded by the President of the United States for technological innovation.

Genzyme's focus on rare diseases had made it very unique in its early history. However, by 2015, many competitors were beginning to explore the "orphan drug" opportunity ("orphan drugs" are those that receive special government protection to target rare diseases). Many large pharmaceutical companies were falling off a "patent cliff"—the patents of large numbers of blockbuster drugs were expiring, leaving companies scrambling to refill their drug pipelines. As a result of this, and the fact that orphan drugs could be sold for extremely high prices and received special protection and incentives, "Big Pharma" companies were now actively pursuing orphan drugs, making the drug market for rare diseases a more hotly contested one.

HUMBLE BEGINNINGS

Genzyme was founded in Boston, in 1981, by a small group of scientists who were researching genetically inherited enzyme diseases. People with these rare disorders (for example, Gaucher disease, Fabry disease, MPS-1) lack key enzymes that regulate the body's metabolism, causing sugar, fats, or proteins to build up in the body and resulting in constant pain and early death. In 1983, the scientists were working out of the 15th floor of an old building in Boston's seedy "Combat Zone," when they were joined by Henri Termeer, who took the role of president and eventually chief executive officer of the company. Termeer had left a well-paying, executive vice president position at Baxter to join the 2-year-old start-up, and many people thought he was crazy to do so.[3] However, Termeer thought Genzyme was well positioned to pursue a novel strategy in the drug industry: target the small markets for rare diseases. Focusing on rare diseases was close to heresy in the pharmaceutical industry. Developing a drug takes 10 to 14 years and costs an average of $1.9 billion to perform the research,

run the clinical trials, get Food and Drug Administration (FDA) approval, and bring a drug to market.[4] Pharmaceutical companies thus focused on potential "blockbuster" drugs that would serve a market that numbered in the millions. A drug was considered a "blockbuster" if it earned revenues of $1 billion or more, and achieving this level required many thousands of patients with chronic diseases such as hypertension, diabetes, or high cholesterol. Genzyme, however, challenged the notion that a firm needed a blockbuster drug to succeed. Genzyme would focus on drugs that were needed by only a few thousand patients with severe, life-threatening diseases.[5] Though there would be few patients for these drugs, there would also be few competitors. Furthermore, the small number of patients and the severity of the diseases would make insurance companies less likely to actively resist reimbursement. Both of these factors suggested that drugs for rare diseases might support higher margins than typical drugs. Additionally, whereas pharmaceutical companies typically needed large sales forces and considerable marketing budgets to promote their drugs, a company focusing on drugs for rare diseases could have a much smaller, more targeted sales approach. There were only a small number of physicians specializing in rare diseases, so Genzyme could go directly to those doctors rather than funding a large sales force and expensive ad campaigns. Finally, therapies with significant clinical value in smaller populations required much smaller clinical trials (though it was more difficult to find the study candidates).

THE ORPHAN DRUG ACT

Genzyme's timing was auspicious. In 1983, the FDA established the Orphan Drug Act to induce development of drugs for rare diseases. The act provides significant tax breaks on research costs and 7 years of market exclusivity to any company putting an orphan drug on the market. This market exclusivity amounted to significantly more protection from rivalry than a typical patent. When a firm secures a patent on a drug, that patent only prevents another firm from marketing the same drug; it does not prevent another firm from marketing a drug that achieves the same or similar action through other means. Thus, when a firm introduced a patented drug that met an important medical need, the race was on by competitors to introduce a different (hopefully improved) version of the drug that could also be patented and compete with the original drug. Drugs for orphan diseases would be shielded from such competition for 7 years, potentially permitting them to recoup their development costs and earn a rate of return that would make the venture attractive.

To qualify for orphan drug status in the United States, a disease had to afflict less than 200,000 people worldwide. Big Pharma was typically uninterested because of the small market sizes and high risks of developing therapies for them. Even most biotech firms failed to see the opportunity inherent in the Orphan Drug Act that might suit their rapidly evolving technologies. Genzyme's eventual success, however, would ultimately attract their attention to this small but lucrative market.

THE FIRST BIG SUCCESS

Genzyme's first commercial product was Ceredase—a replacement protein designed to treat fewer than 10,000 people afflicted with a deadly, rare, genetic disorder called Gaucher's disease. Children born with this disease rarely live past their 10th birthday, and adults who develop this fatal disease suffer from chronic, liver, kidney, heart, and spleen damage. Clinical trials for Ceredase began in 1984, and in March 1985 the FDA designated Ceredase an orphan drug. Genzyme was first allowed to make Ceredase available to patients outside of the United States in 1990, and was approved by the FDA to market Ceredase in the United States in 1991.

Creating a therapy to treat a patient with Gaucher's disease required extracting proteins from human tissue, and the most productive source of these proteins was found in human placentas. The expense and difficulty of this provided a substantial barrier to competitive entrants. Not many experts believed Genzyme could be commercially successful with this product. As Termeer noted, "The FDA thought we were out of our minds." In an interview, he explained:

> The hurdles to raise more finance for the trials were formidable. Not least was the fact that human placentas were the source of the enzyme

and to provide a year's dose for just one patient, more than 22,000 placentas were needed. To overcome this, Genzyme built a plant in France to take unwanted placental tissue which would have otherwise been burnt and extracted the enzyme. At one point 35% of all placentas from the United States were passing through the French plant. Ceredase was the only drug made from placentas that the U.K. government allowed to be used in Britain.[6]

By 1991, Genzyme was collecting a million placentas a year, and knew it could not produce enough of the enzyme to treat all the patients who needed it. Fortunately, by 1993, Genzyme had developed a recombinant form of the enzyme, Cerezyme, which obviated the need for human tissue and made efficient production possible. In the meantime, Genzyme had also begun work on gene therapies and begun investigating potential treatments for another rare enzyme disorder, Fabry disease.

REMAINING INDEPENDENT

Genzyme also broke with industry norms in its decision to *not* work with large pharmaceutical companies. Whereas most biotech companies licensed their technologies to large pharmaceutical firms to tap the larger companies' greater capital resources, manufacturing capabilities and marketing and distribution assets, Termeer felt strongly that the company should remain independent, stating, "If we worked with a very large corporation, we would lose our strategic direction and be dependent … we've tried to stay as self-sufficient as we possibly can."[7] Performing its own testing, manufacturing, and sales meant incurring much greater risks, but it also meant that the company would keep all of the profits its drugs earned. To generate revenues to fund the research, Termeer entered into a number of side ventures, including a chemical supplies business, a genetic counseling business, and a diagnostic testing business. He also took the company public in 1986, raising $27 million. Termeer's gamble paid off: Patients taking Cerezyme paid an average of $170,000 a year for their medication, and with about 4,500 patients committed to taking the drug for life, this amounted to more than $800 million in annual revenue from Cerezyme alone.[8]

THE COMPETITION IN BIOTECH

The global biotechnology industry included about 10,000 companies in 2015, with total revenues of about $289 billion.[9] Major players included U.S-based Gilead Sciences ($24.9 billion), Amgen ($20 billion), Monsanto ($15.9 billion), Biogen Idec ($9.7 billion), and Genentech (owned by Switzerland-based Roche, $50.4 billion), as well as Australia's CSL ($5.3 billion), Germany's Merck KGaA ($15.3 billion), Denmark's Novo Nordisk ($15.4 billion), and the biotech research arms of major international pharmaceutical companies.[10] Genentech was the oldest, formed in 1976; Amgen and Genzyme were established in the early 1980s. Many competitors were small, emerging companies with less than 500 employees. In fact, more than 50 percent of biotech companies had fewer than 50 employees.[11]

Most biotech start-ups followed a similar path of evolution. The firm would begin as a research and development firm, with employees coming from university science labs or Big Pharma. If the start-up survived the lean years and had prospects for producing a commercially viable therapy, it would seek alliances with large firms for late-stage development, manufacturing, and marketing. For example, both Genentech and Gilead formed relationships with Roche, and Amgen formed a relationship with Abbott Laboratories. If a firm's drugs achieved commercial success, it could negotiate higher royalties and attract capital investment.

Genzyme differed from all its peers and from later biotech companies by being profitable early on (Genzyme posted a profit of just over $20 million in 1991, losses in 1992 and 1993, and a profit of over $16 million in 1994), and until only recently, remaining independent of partners. "We wanted a diversified company that could use technology to make a difference for people with serious diseases, and to get profitable so we can continue to develop new medicines," Termeer said.[12] In the late 2000s, most analysts believed that no other developer was likely to pursue

Genzyme's strategic path, even with the benefits offered under the Orphan Drug Act. While both Amgen and Genentech had produced orphan drugs, it had not been their strategic focus.

THE GROWING COMPETITION IN ORPHAN DRUGS

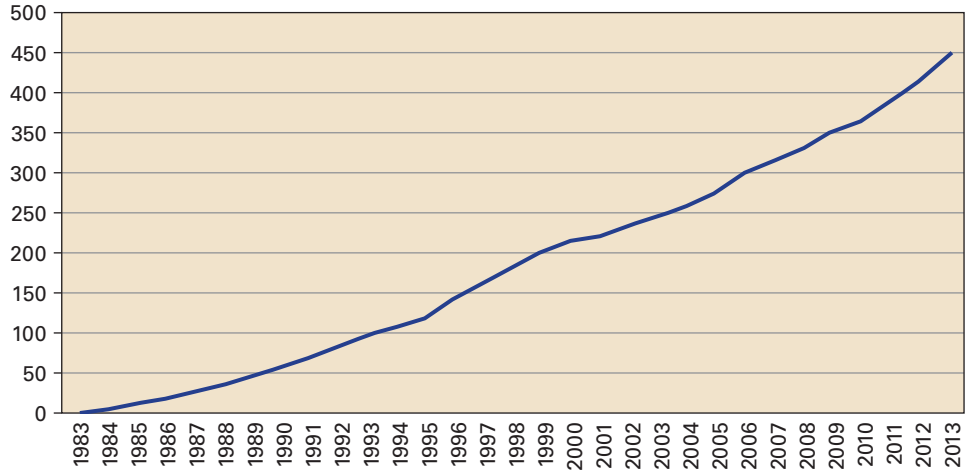
It is estimated that there are between 5,000 and 8,000 known rare diseases in the world. In the decade leading up to 1983, only 10 orphan drugs entered the market according to the FDA. However, from passage of the act until the end of 2013, 447 orphan drugs were approved by the FDA (see Figure 1). The European Union passed similar legislation protecting "orphan medicinal products," granting them market exclusivity for 10 years after approval. Japan, Singapore, and Australia also began offering subsidies and other incentives to develop drugs for rare diseases. As of 2010, roughly 200 orphan diseases had become treatable.[13]

Genzyme had proven that a business could be built around small disease populations and demonstrated its ability to profitably serve markets that seemed financially unjustified. Even large pharmaceutical companies struggling due to the "patent cliff" began to pay more attention to the orphan drug opportunity. While this was good news for sufferers of rare diseases, it meant significantly more competition for Genzyme. Companies such as Pfizer, Isis Pharmaceutical, NPS Pharmaceuticals, GlaxoSmithKline, and Shire were all beginning to target orphan drugs. As noted by Francois Nader, chief executive of NPS Pharmaceuticals, shifts in science and economics had made the orphan drug market more viable. Researchers could identify ahead of time "the patients that would benefit from a particular drug, rather than using the shotgun approach we used in the past."[14] Ironically, despite the small numbers of patients served, high prices enabled almost one-third of orphan drugs to achieve $1 billion in sales[15]—making them the new blockbusters.

INDEPENDENCE NO MORE

Growing competition wasn't the only challenge Genzyme was facing. A series of manufacturing problems created shortages that impaired its sales of Cerezyme and Fabrazyme in 2009 and 2010. To make matters worse, plant contamination problems caught the FDA's attention in 2010, resulting in fines and sending the stock into a tumble, making the company vulnerable to a takeover. Switzerland-based pharmaceutical company Sanofi, one of the largest

Figure 1 Cumulative Number of U.S. FDA Orphan Drug Approvals, 1983–2013



pharmaceutical companies in the world,[16] began making overtures. Genzyme rebuffed the initial offers,[17] but after months of negotiation Genzyme was acquired by Sanofi for $20.1 billion in February 2011, ending its 30-year run as an independent biotechnology drug maker. Henri Termeer resigned, and Sanofi CEO Christopher Viehbacher took over. The company retained its name and its facilities in Cambridge, Massachusetts, becoming Sanofi's new headquarters for rare diseases. With the backing of Sanofi, Genzyme was able to expand its manufacturing capabilities, opening up a manufacturing plant in the United States and expanding its production facility in Ireland.

In September 2012, the FDA approved Genzyme's first multiple sclerosis drug, Aubagio, a once-daily oral drug, and in November 2014 the FDA approved Genzyme's second multiple sclerosis drug, Lemtrada, an intravenous drug delivered through two sets of injections, a year apart.[18] Unlike Genzyme's other targeted diseases, multiple sclerosis was not rare: 2.3 million people were estimated to suffer from it worldwide, including 400,000 in the United States.[19] The two drugs made Genzyme—and parent Sanofi—among the most visible competitors in multiple sclerosis treatments. Genzyme had also proven to be among the fastest-growing holdings of Sanofi, rapidly earning far more than the $20.1 billion Sanofi had paid for it, and significantly boosting Sanofi's stock price. When Sanofi had acquired Genzyme in February 2011, its stock had traded at roughly $34 a share; by late 2014, the stock was trading at over $50 a share.[20] As noted by Sanofi CEO Chris Viehbacher, "Once we had Genzyme, that changed investor perception about Sanofi … It significantly increased the visibility of Sanofi in the United States. It signaled that Sanofi was a company that was serious about biotechnology and research and development."[21]

NOTES

1. Adapted from a New York University Teaching Case by Jane Cullen and Melissa A. Schilling.

2. Company website: http://www.genzyme.com/corp/structure/awards_genz.
3. S. Calabro, "The Price of Success," *Pharmaceutical Executive* 26 (3) (2006): 64–80.
4. Standard & Poor's Industry Surveys, 2013.
5. N. Watson, "This Dutchman Is Flying," *Fortune* (Europe) 148 (1) (2003): 55–57.
6. "Ten Years of Enzyme Replacement Therapy," www.gaucher.org.uk/tenyearsapr03.htm, retrieved April 21, 2006.
7. N. Watson, "This Dutchman Is Flying."
8. D. Shook, "Biotechs Adopt the Orphan-Drug Market," *Businessweek* Online, December 13, 2002.
9. Global Biotechnology: Market Research Report. IBIS World, January 2015.
10. Hoovers, accessed March 12, 2015.
11. "Top Biotech Companies by 2005 Revenue," www.bioworld.com/img/TopDrugs_sample.pdf.
12. C. Robbins-Roth, *From Alchemy to IPO: The Business of Biotechnology* (New York: Basic Books, 2000), p. 44.
13. W. Armstrong, "Pharma's Orphans," *Pharmaceutical Executive*, May 2010. www.pharmexec.com
14. J. D. Rockoff, "The Big Business of Orphan Drugs," *The Wall Street Journal*, January 31, 2013, p. B.1.
15. Ibid.
16. A. K. Fathima, "Forbes Global 2000: Biggest Drug Companies in the World; Pfizer Tops List," *Forbes*, June 25, 2014. www.forbes.com
17. J. Jannarone, "Genzyme's Time Out with Sanofi," *The Wall Street Journal*, September 28, 2010, p. C.10.
18. www.fda.gov, accessed March 19, 2015.
19. J. Walker, "Sanofi's Genzyme Gets FDA Approval for MS Drug; Lemtrada Will Only Be Available in the U.S. Through a Restricted Distribution Program," *The Wall Street Journal Online*, November 15, 2014.
20. Finance.Yahoo.com, accessed March 9, 2015.
21. R. Weisman, "Sanofi Chief Says Genzyme Purchase Paid Off," *Boston Globe*, September 19, 2013. www.bostonglobe.com