

MARCH 2006

FOR GLOBAL BUSINESS AND MARKETING LEADERS

# Pharmaceutical Executive

Genzyme:

## WHO WILL PAY?

WHEN YOU MAKE THE WORLD'S MOST EXPENSIVE DRUGS,  
YOU HAVE TO WONDER...

CEO Henri Termeer



Cover Photography by John Halpern

## COVER STORY

# The Price of Success

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Genzyme spent \$2 million per patient on developing its latest drug. Efficacy is a given. Access is the question.

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A portrait of Henri Termeer, CEO of Genzyme, sitting in a bright red, modern-style chair. He is wearing a dark brown suit jacket, a light blue shirt, and a striped tie. He has his hands clasped in his lap and is smiling at the camera. The background shows a modern office interior with large windows and a glass railing.

Genzyme's CEO,  
Henri Termeer:  
"We're going to  
be successful on  
the basis of who  
we are."



**T**wo days before I went to visit Genzyme, Theo Epstein, general manager of the Boston Red Sox, announced his resignation. Epstein became an icon in October 2004, when his team won its first World Series since 1918. Sox fans or not, people everywhere were stunned by what he had accomplished at such a young age—Epstein was 30 when the Sox took home the pennant, and just 28 when he was named to the top post. But to Bostonians, Epstein was special not just because he climaxed professionally before most people get going, but also because of his willingness to do things his own way. The people of Boston loved Theo for his guts: About seven months into his tenure, in a defining moment, Epstein traded star shortstop Nomar Garciaparra for two comparatively unknown players, Orlando Cabrera and Doug Mientkiewicz. Fans squealed. Radio talk show hosts predicted the team's demise. Players feared they'd been doomed. But Epstein stood

Genzyme put patients first,  
and grew to become  
a multi-billion-dollar company.  
But empires don't survive  
on altruism.

# The Price of Success

BY SARA CALABRO, MANAGING EDITOR | PHOTOGRAPHY BY JOHN HALPERN

by his decision. And a few centerfield smacks by Cabrera later, he had the whole town standing beside him.

Given the general sentiment toward Epstein, it's no surprise that several people I met with from Genzyme broke the ice by commenting on his decision to leave the team. All Boston-area residents, Genzyme executives were as susceptible as anyone to the citywide crush on this boy wonder—maybe even more so. Genzymers, perhaps, felt a kinship with Epstein.

Like the Red Sox's general manager, Genzyme, against odds, combined instinct, passion, and market knowledge to grow an enterprise. Both ventures involved risks, but only calculated ones: Epstein didn't arbitrarily trade Garciparra; he did it to improve the team's poor defense. Genzyme priced its drugs at jaw-dropping heights, but not without a plan for structured access programs. Both Epstein and Genzyme soared in the face of criticism: Epstein overcame age discrimination and disagreement over trading decisions to accomplish the unthinkable. Genzyme also has done the unthinkable—built a hugely profitable business by developing life-saving treatments for thousands (not millions) of rare-disease victims. Neither hero has ever said, "I'm sorry."

It is easy to see why Epstein's decision might strike a chord in Genzyme executives. After all, they are witnessing first hand the company's evolution from start-up to multi-billion-dollar machine. For 25 years, the spirit of Genzyme has been a matter of humble beginnings, market exclusivity, and putting patients first. The company still preaches these things, but in many ways—like Epstein, who is rumored to have stepped down to get out from under his mentor's wing—Genzyme has outgrown its foundation. Dwindling holds on monopolies, pressure to recoup international investments, and intense scrutiny of prices raise questions about whether the company's strategy for rising to the top can be sustained long term. When Theo Epstein announced he was leaving, Genzyme executives had one more reason to ask a scary question: Would newfound prosperity force them, like Epstein, to abandon a proven model of success? And an even scarier one: Where to go from here?

## Seeing Green

When CEO Henri Termeer was recruited to join Genzyme, in 1983, the company was working from the 15th floor of an old Garment District building, in Boston's Combat Zone, the city's seedy red-light district.

"You would park the car, and you would get propositioned three or four times before you got to the office," says Termeer. "It was all very romantic in a sense."

Termeer himself is romantic. His eyes are squinty, like he's getting a closer look. His stare suggests he knows something you don't. He speaks with a thick accent (he's Dutch), almost in a whisper.

"People would visit me in these modest digs," says Termeer of Genzyme's first office, "and they would say, 'What happened to you? Where is your sense?'"

Termeer left a well-paying executive-vice-president job with Baxter, where he'd been for 10 years, to go to the then two-year-old start-up. He'd been working in Southern California, which Termeer says always felt temporary: "Nobody deserved to live in such nice conditions."

Termeer finds himself in pretty nice conditions now. The company recently spent \$140 million to build its new headquarters in Cambridge, Massachusetts. The day I arrive there, I stand among environmental groups, contractors, and students, who wait to tour what the Association of General Contractors called

"one of the most environmentally responsible office buildings ever built in the United States." Today is no exception. Genzyme executives make a habit of mentioning the frequent tour groups that come to see their creation, where reflective pools and full-sized trees fill the entryway, and window blinds automatically adjust to absorb heat from the sun.

I ascend to Termeer's office suite in a glass elevator. His assistants greet me in a private foyer, and guide me to the CEO's adjoining personal meeting room. On this cool afternoon, the glass doors to the terrace are closed. A few minutes later, he joins me. Cool and collected, Termeer quickly gets into Genzyme's early days in less opulent quarters: "It's amazing how

much confidence you can talk yourself into," he says. What initially comes off as arrogance in Termeer actually makes him likeable. The more he talks, his aloofness turns to shyness; his ego seems bold—admirable.

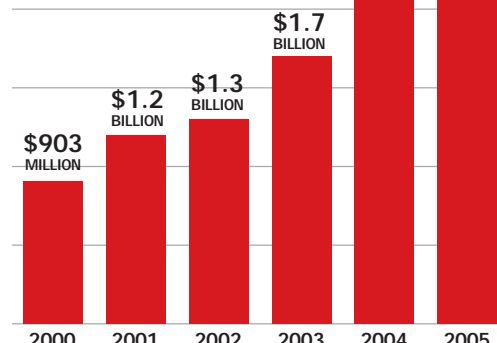
**Adopting orphans** It's this boldness that inspired Genzyme to capitalize on a new piece of legislation that addressed rare-disease drug development. The Orphan Drug Act, which was signed into law in 1983, grants seven-year exclusivity to companies that make drugs for "orphan" diseases (those that affect fewer than 200,000 people in the United States), and allows them to tax-deduct a portion of clinical trial costs. With this in mind, Genzyme launched clinical trials in 1984 for Ceredase (alglucerase injection), an enzyme replacement therapy for Type 1 Gaucher disease; the product won FDA approval in 1991. Three years later, Genzyme introduced Cerezyme (imiglucerase for injection), a second-generation recombinant product, which, over a decade later, remains the only drug of its kind, and Genzyme's biggest moneymaker.

Based on a strategy of developing therapies for astonishingly small patient populations and commanding some of the highest prices in the drug-making world, Genzyme has tripled its revenues in five years, from \$900 million in 2000 to \$2.7 billion in 2005.

The company's flagship products treat a family of diseases

## Rising Profits

Genzyme has tripled revenue in five years.



source: Genzyme annual report

A PharmExec Graphic (jli)

known as lysosomal storage disorders (LSDs), which typically affect fewer than 10,000 people worldwide and are caused by enzyme deficiencies. Genzyme markets three enzyme-replacement therapies—Cerezyme; Fabrazyme (agalsidase beta), for Fabry disease; Aldurazyme (aronidase), for Mucopolysaccharidosis I (MPS I)—and is developing a fourth, Myozyme (alglucosidase alfa), for Pompe disease. In 2005, LSDs brought in \$1.3 billion, or 48 percent of Genzyme’s total revenues. Cerezyme accounted for most of that, pulling in \$932 million. Fabrazyme jumped 45 percent from 2004, to \$305 million. And Aldurazyme chipped in \$77 million, up 80 percent from the year before.

**Cash cow** Cerezyme costs \$200,000 per patient, per year. Patients who need the drug, which is given as an infusion every two weeks, must take it for life. Genzyme’s other LSD treatments, Fabrazyme and Aldurazyme, both approved in 2003, also are very expensive, each costing on average between \$175,000 and \$200,000 a year per patient.

Those prices—especially Cerezyme’s, because of how long it’s been on the market—have attracted some unfavorable attention to Genzyme. Last November, *The Wall Street Journal* ran three scathing articles—two of them on Page One—on the company’s pricing strategies. Genzyme, though, is unapologetic. “We have to explain that our drugs are expensive, but I don’t mind explaining it,” says Termeer. “We try not to have massive price differentials between markets. We try to be very insistent on access, making sure we don’t abuse the monopoly situation we’re in.”

Indeed, the company argues that it has been steadily reducing the real cost of Cerezyme by holding the price steady in the United States since launch. “As a rule, the pharmaceutical industry will increase its price a couple percentage points every year,” says David Meeker, Genzyme’s president of LSD therapeutics. “When you factor in CPI [consumer price index] increases, we have had a real price decrease by holding dollars constant.”

Not everyone sees it that way. Abbey Meyers, president of the National Organization for Rare Disorders, a coalition of about 130 voluntary health agencies that work for different rare diseases, remembers the switch from Ceredase, the first-generation treatment, to Cerezyme. “Genzyme said, ‘Ceredase is so expensive because it’s so hard to get these placentas. When we create a way to make it in big vats through biotechnology, it’ll be less expensive,’” says Meyers. (Enzymes for Ceredase were produced from human placentas; it took 22,000 placentas to make enough

enzyme to treat one Gaucher patient for a year.) “When they came out with Cerezyme, somebody from the company called up saying, ‘You’re going to be so proud of us. We are not charging any more for Cerezyme.’ I could not believe my ears. They’re charging the same as they did for the original drug, even though they’re manufacturing in larger quantities.”

To that, Meeker says, “People get very focused on thinking it’s got to be costing us less to make after 10 years. The answer is, yes, it does cost us less to make it, but it still has a significant cost. There are so many different pieces that are part of making sure patients can access the drug.”

Manufacturing is a big part of the price tag. LSD drugs are complex biotech products that require expensive equipment and long manufacturing cycles. The company is currently building a six-story, \$124 million research lab in Framingham, Mass. The lab is part of a \$210 million manufacturing- and research-expansion project that includes a research facility in Waltham, Mass., and \$53 million of additions within the company’s protein-manufacturing plant in Allston, Mass. Genzyme also is investing in manufacturing overseas, with three expansion projects happening in Ireland and the United Kingdom, and a new plant that opened in September 2005 in Geel, Belgium. Together, the international projects represent capital investments of more than \$500 million dollars.



**REFLECTING** Twenty-two-million dollars of the total building costs for Genzyme’s new headquarters went toward making it “green,” or environmentally responsible. Here, CEO Termeer looks up at the entryway’s hanging prisms, which resemble falling graduation caps and reflect rainbows throughout the building.

# Joint Effort

After about a decade on the job, CEO Henri Termeer divided Genzyme's assets into three tracking stocks—Genzyme General, Genzyme Biosurgery, and Genzyme Molecular Oncology. The tactic was intended to highlight the financial performance of separate divisions, but it ultimately became a distraction to investors. Effective July 2003, Genzyme did away with the system and consolidated under Genzyme Stock, which reflects the performance of six business units.

**Therapeutics** Products in this division treat patients suffering from genetic and other chronic debilitating diseases. In this category, Genzyme markets Cerezyme, for Type 1 Gaucher disease; Fabrazyme, for Fabry disease; and Aldurazyme, for Mucopolysaccharidosis I (MPS I). Myozyme, for Pompe disease, is expected to launch this year. Thyrogen (thyrotropin alfa for injection) is a follow-up thyroid cancer treatment. In 2005, the unit brought in \$1.3 billion, or 48 percent of total revenues. Cerezyme pulled in \$932 million, accounting for about 71 percent of the division's revenue. Fabrazyme made \$305 million, Aldurazyme \$77 million, and Thyrogen \$78 million.

**Renal Disease** The company's second-most-profitable category brought in \$452 million in 2005. The biggest seller is Renegel (sevelamer), a metal- and calcium-free phosphate binder; it made \$417 million in 2005. Genzyme bolstered its renal business in July 2005, when it acquired Bone Care International for \$600 million. Along with that deal came Hecetrol (doxercalciferol), a pro-hormone vitamin D2 formulation for chronic kidney disease. Fourth-quarter sales of Hecetrol only reached \$20 million, but Genzyme just started marketing it in July. The product only has US approval, so far.

**Orthopedics/Biosurgery** This division grew 68 percent from 2004 (\$210 million) to 2005 (\$353 million). The jump is due largely to Synvisc (hylan G-F 20), a pain treatment for osteoarthritis of the knee. In January 2005, Genzyme acquired from Wyeth full sales

and marketing control of Synvisc in the United States and several European countries. Synvisc revenues reached \$219 million in 2005. Also in this category are Carticel (autologous cultured chondrocytes), for repairing damaged knee cartilage, and Septra, a line of anti-adhesion products.

**Genetics/Diagnostics** Genzyme's genetic-testing services—which focus on prenatal, post-natal, and oncological testing—and diagnostic products are an increasingly important part of the company's business. The division brought in \$327 million in 2005 (\$223 from services and \$104 from products), an increase of 17 percent from 2004.

**Transplant and Immune Diseases** Transplant is the only unit that did not grow from 2004 (\$151 million) to 2005 (\$146 million). Products include Thymoglobulin (anti-thymocyte globulin, rabbit), which made \$116 million in 2005, and Lymphoglobuline (anti-thymocyte globulin, equine), for acute rejection in kidney transplants.

**Other** Revenue from other ventures jumped 64 percent, to \$135 million, in 2005 compared with 2004. Campath (alemtuzumab for injection), for B-cell chronic lymphocytic leukemia, and Clolar™ (clofarabine), for children with refractory or relapsed acute lymphoblastic leukemia, brought in \$47 million in combined revenue. Also included in this category are sales of pharmaceutical intermediates, R&D revenue, and royalties from the sale of WelChol (colesevelam), a cholesterol-lowering drug.

But an even more significant contributor to costs is R&D. Every drug maker faces high R&D costs, but Genzyme's per-patient spending puts the company in another class. Rare-disease trials, says Meeker, “are more complicated because you have so few patients, so you need to get the maximum amount of information from those few. You can compensate for that if you have thousands of patients, because the numbers do the work for you.” Trials for enzyme replacement treatments require biweekly, on-site infusions that take several hours. To get the drugs approved, complex measures, such as a heart, kidney, and skin biopsies, must be taken.

**Myozyme** Take the company's leading pipeline candidate, Myozyme. The drug is an enzyme replacement therapy for Pompe disease, a currently untreatable condition that causes weakened muscles and difficult breathing. Pompe affects adults, but it is most common—and devastating—in children.

“These are kids who, when they should be sitting, they cannot sit,” says Georges Gemayel, executive vice president of therapeutics, renal, and transplant at Genzyme. “They are just slumped; they fall on themselves. These are kids who, very quickly, stop being able to breathe on their own.”

Ninety percent of children with infantile-onset Pompe die within before their first birthday, which made it extremely difficult to enroll the trial. “We enrolled 18 patients,” says Meeker. “To get in, they had to be diagnosed and enrolled before [they were] six months [old]. The average age that a child is diagnosed is around three months. We had between three and six months.”

Genzyme covered travel costs for children and families from Palestine and Japan who had to be flown to trial sites. Manufacturing costs also are especially high, because Myozyme is administered at such a high dose (about 20 times that of Fabrazyme).

The company is working on ways to reduce the cost of trials. One example is newborn screening, which would help identify at least new patients with diseases like Pompe. The plan is to provide reagents for newborn screening free of charge to any public institution that does the testing. By giving the reagents for free, Genzyme hopes the institutions will become part of a newborn screening program that identifies patients early on that are likely to develop a need for drugs like Myozyme. As soon as the biological need develops, treatment can be activated.

But even with improvements, there are still a limited number of patients over which to spread the cost. Total development costs for Myozyme were \$500 million. So far, only 200 people, scattered throughout 14 countries, have been identified as needing the drug. That's more than \$2 million per person. However it is priced (the company has made no announcement so far), Myozyme can't be cheap. Someone has to pay. The question is who—and how can they be persuaded?

## Buried Treasure

Because it works with such tiny patient populations—and because its drugs are a matter of life and death for the people who take them—Genzyme has been forced to come up with its own solution to the eternal problem of pricing and access. This strategy, according to Termeer, is what's allowed Genzyme to sustain such a high price point. “The difficulty for the pharmaceutical industry has been that it developed life-saving drugs,

like for HIV, and then didn't look after the access question carefully enough," he says. "We didn't fall into that trap."

On the access side of the equation, everyone who needs Cerezyme gets it, regardless of their ability to pay. Currently, 4,500 people take the drug, and about one-tenth get it at no cost. "I've never heard anyone say 'so and so family can't get [Cerezyme]," says Sharon Terry, president of Genetic Alliance, a coalition of about 600 disease advocacy organizations. Terry says Genzyme is the "most responsible, most responsive" company she has worked with in terms of helping patients gain access to drugs.

On the price side, the company works with a radically simplified policy. "There are essentially two prices," says Termeer. "There's X and there's free."

Genzyme considers this the fairest approach. In the company's experience in dealing with health ministries, countries seek to negotiate price points on the basis of what other countries (typically the ones where the drugs are priced the lowest) are paying. Genzyme acknowledges its commitment to helping patients in countries that can't pay for expensive drugs. But, says Meeker, "It's with an eye toward moving them toward independence."

In negotiating, the company looks for a commitment on the part of the country: Perhaps Genzyme provides drugs and the government supports a center of excellence or educational programs. Or, Genzyme provides drugs to children while the

**GENZYME HAS AN IMPRESSIVE INTERNATIONAL RECORD IN REGIONS WITH INTACT HEALTHCARE SYSTEMS. BUT SO FAR, ALGERIA IS ONE OF VERY FEW COUNTRIES WHERE GENZYME'S DRUGS HAVE GONE FROM FREE TO PAID FOR. THE COMPANY IS BASING A HUGE INVESTMENT ON FAITH.**

country pays for adults. One of the company's more established efforts is the Gaucher Initiative, a program sponsored by Genzyme and operated by Project HOPE that donates Cerezyme to patients in Vietnam, Sri Lanka, Tanzania, and other countries where no healthcare system supports it. As of January 1, 2006, 213 patients in 16 countries were receiving treatment this way. In addition to the Gaucher Initiative, Genzyme sponsors something similar, the European Cerezyme Access Program, to assist Gaucher patients in Eastern Europe. This program currently donates Cerezyme to 65 patients in eight countries. These gestures are performed under the assumption that at some point, the developing country's government will begin providing reimbursement.

"Things that are free have no value," says Meeker, "so the idea of dropping a drug off at the border isn't the goal. The goal is to create a sustainable healthcare system that overtime can take care of its patients with rare diseases."

That's an ambitious goal, one that some people doubt can be pulled off. But Genzyme points to Algeria. In July 2004, the Central Pharmacy of Algeria placed its first order for Cerezyme, to be reimbursed by the Algerian National Health Care System, for a patient formerly receiving the drug for free through the Gaucher Initiative. The patient was approved for inclusion in the program in 2001, when he was five years old, since Algerian govern-

ment couldn't pay for the therapy. In late 2003, Genzyme partnered with external organizations to lobby for and promote Cerezyme in Algeria. Their work, combined with changes in Algerian health policy, persuaded the Algerian Ministry of Health to authorize the importation and reimbursement of non-registered orphan drugs like Cerezyme.

Following the authorization, Genzyme organized a "Gaucher Day" in Algeria to discuss next steps. The event attracted more than 80 Algerian specialists with experience in the disease, as well as members of the Ministry of Health, the National Health Care System, and the Central Pharmacy. Collaborations at the event resulted in a list of nine previously unidentified Algerian patients who need access to Cerezyme.

Genzyme is hoping for similar success in bigger countries, but what worked in Algeria may not work on a larger scale. China, India, Latin America, and Southeast Asia are current regions of focus. More established Latin American countries, like Brazil, Argentina, and Columbia, are already reimbursing Genzyme for its products. But in places like Ecuador and Cuba, drugs are donated. Same thing in Asia: Japan, Hong Kong, and Korea pay for the drugs, while China, the Philippines, Malaysia, and Indonesia do not.

Historically, Genzyme has done well in its international endeavors. Sandy Smith, president of the company's international group, who spent 14 years with Bristol-Myers Squibb earlier in his career, says Genzyme's sense of global awareness has given it an advantage. At Big Pharma companies, he says, "models tend to be replicated from country to country." In contrast, Genzyme has been successful internationally because it has "tailored the individual markets' structures to what we need to serve the patients," says Smith. "That's been the driving force of how we've done things."

Indeed, Genzyme's overseas track record—about 50 percent of revenues come from outside the United States—is above average. But, that international success has occurred in countries with intact healthcare systems. Thus far, Algeria is one of very few countries where Genzyme has been successful in developing the kind of reciprocal relationship it is after, where a government that did not previously support reimbursement for therapy starts paying. (Genzyme also worked with health officials in Romania, population 22 million, to come up with a plan for including Cerezyme in its annual healthcare budget.)

China A prime target today is China, where 100 Gaucher patients currently receive Cerezyme for free. Enthusiastic about the prospects there, Genzyme recently opened an office in Shanghai, and plans are underway to open in Beijing.

"China is 1.3 billion people," says Smith. "There are about 13 cities that are projected in the next five years to have a middle class that can access Western-style medicines. So you're talking about 100 million people that could—and will, based on existing growth and the infrastructure of China—be potentially needing our products."

But consider: In Algeria, a country of only 30 million people, the number of Gaucher patients wanting Cerezyme

increased nine-fold once communications efforts within the region improved. It's reasonable to expect the number of patients receiving free Cerezyme in China to increase at a similar rate (or higher, given China's inherent advantages over Algeria due to size). That leaves 900 people, at minimum, needing the drug. In accordance with its "everyone-who-needs-it-gets-it" policy, Genzyme will have to give away \$180 million worth of Cerezyme per year, until the Chinese government decides to reimburse for the drug—a milestone that Termeer admits will take at least a decade to accomplish. That's \$1.8 billion over 10 years for just one drug, in one country.

That's a huge investment (by comparison, Genzyme gave away only \$46 million worth of all drugs combined in 2004), but Termeer says it's okay. "Anything that you engage in from the beginning will take ten, fifteen years to amount to anything." China is "starting from scratch," he says. "We need to be on the ground in a multi-functional sense—not as a cheap resource, but as a participant in building the market."

### Managing Care

In the United States, the job of getting reimbursement for Cerezyme has been relatively straightforward. Most patients are covered in full by their insurance policies. Patients who need help dealing with their coverage can turn to Genzyme Treatment Support (GTS). The group is made up of case management specialists, who help patients review their current insurance policies and, if necessary, work with them to obtain additional coverage to maintain long-term therapy. GTS also supports patients who need Fabrazyme and Aldurazyme.

Rhonda Buyers, executive director of the National Gaucher Foundation, the disease's foremost support group, says the feedback she's received from patients indicates GTS is an effective system. "Once [patients] have been identified," she says, getting access to treatment "can be a very fast process—certainly if their insurance company is already paying for other Gaucher patients."

For US patients who don't have insurance, Genzyme offers the Charitable Access Program through which Cerezyme, Fabrazyme, and Aldurazyme are provided for free. There is no cap on the number of people who can be in the program at a time (as of January 1, there were 37), but it is temporary. Patients and their families are expected to continue exploring alternative funding options while Genzyme pays for their treatment.

So far, payers have been good about paying for Genzyme's

super-expensive products. This is partly because there are so few patients who need the drugs, and therefore, the collective impact on individual insurance companies is minimal. It's also because the drugs work.

"The incremental cost associated with this aspect of medicine is less than a fraction of a percent" of overall healthcare costs, says Termeer. Excessive healthcare costs, he says, "are associated with what we cannot treat. The costs that are associated with things that really work are relatively small."

Indeed, effectiveness of treatment is increasingly becoming the number-one consideration in insurance companies' coverage decisions, says Mohit Ghose, vice president of public affairs for America's Health Insurance Plans, an industry trade group. "It's not a question of providing coverage for these high-end biotech," he says. "It's a question of whether a drug is the best in a particular situation."

In January, the Centers for Medicare & Medicaid Services (CMS) expanded coverage of implantable cardioverter defibrillators, a move that points to a trend in insurance coverage. With Medicare moving in the direction of paying for higher-end products, yet requiring comparative analysis and post-marketing surveillance, Ghose says health plans are anticipating a "continued evolution" toward coverage for the most expensive treatments, as long as they are shown to be best in class.

If that's the case, Genzyme currently is in a pretty good spot.

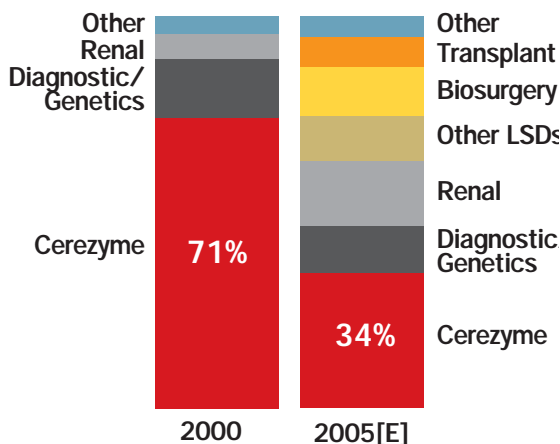
"You're talking about a population for whom the alternative to not receiving therapy is serious morbidity or mortality," says Antony Pfaffle, an analyst with Black Diamond Research.

That's true—for now—in LSDs, but as Genzyme diversifies itself (see "Diversification"), it'll have to work harder to win comparative effectiveness arguments. The company currently operates across six business units (see "Joint Effort," page 8). None are as lucrative as therapeutics, where LSDs reside, but with Genzyme's prized rare-disease markets attracting competition, the company must adjust.

### Facing Reality

Drug companies, traditionally, haven't spent much time battling over patient populations of a few thousand. But Genzyme has felt some heat from potential competitors. In 2001, as Genzyme's Fabrazyme neared approval, it was running neck and neck with another Fabry treatment—Replagal, developed

## Diversification



In 2000, Cerezyme accounted for 71 percent of revenues. Today, the drug only makes up 34 percent. But the numbers can be deceiving: Genzyme isn't making any less money from Cerezyme today than it was five years ago. In fact, the 34 percent it contributed in 2005 (\$932 million) is about \$30 million more than what Genzyme made in 2000 from all products combined. This, what critics call an exorbitant amount of money, is what Genzyme says has allowed the company to continue developing new treatments for other rare diseases.

source: JP Morgan Healthcare Conference presentation, January 9, 2006

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by Transkaryotic Therapies (TKT). Both products were approved in Europe in August, and the companies faced off for US rights. (According to the rules of the Orphan Drug Act, the first product to win approval for an orphan indication is awarded the exclusivity.) In April 2003, FDA approved Fabrazyme over Replagal, giving Genzyme a significant advantage in the category. TKT was purchased in July 2005 by another Genzyme competitor, Shire, maker of Fosrenol, which competes with Genzyme's phosphate binder, Renegal.

Today, Shire Human Genetic Therapies (HGT), as TKT is now known, is targeting Genzyme's most important product, Cerezyme. While there is at least one other treatment for Gaucher disease—Actelia Pharmaceuticals' Zavesca (miglustat), an oral treatment for adult Type 1 Gaucher patients for whom enzyme replacement therapy is not an option—that drug has never competed directly with Cerezyme, because the dose in Zavesca is lower and enzyme replacement therapy is considered the standard of care.

Shire HGT's new product, gene-activated glucocerebrosidase (GCB), also is an enzyme replacement therapy, but it's derived from human cell lines rather than from hamster cells like Cerezyme—a distinction Shire HGT sees as critical, although it won't say why. This fall, Shire HGT released positive six-month data from a Phase II clinical trial of GCB, and the company is shooting for approval in 2008. It poses the most direct threat yet to Cerezyme—and Genzyme.

Shire HGT is tight-lipped about the potential of its product, but Michael Hall, the company's vice president of research, says competition intrinsically benefits sufferers of rare diseases. "Sometimes patients run into difficulties with one product and they tolerate a second one better," he says. "There may be preferences in clinical practice that dictate one clinician wanting to provide one product over another. And in terms of product availability, having more than one in the market may allow broader formulary access."

There are even some potential benefits for Genzyme. Competition is likely to improve awareness of Gaucher, something that Genzyme has had to handle alone. A competitor would

## New Ground

of revenues. But most pipeline activity falls outside Genzyme's traditional areas of expertise, potentially posing development and marketing challenges.

**Campath** In partnership with Schering AG, Genzyme plans to initiate this year Phase III clinical trials to evaluate this B-cell chronic lymphocytic leukemia drug for multiple sclerosis. The drug also is being studied for non-Hodgkins lymphoma.

**Clolar** Genzyme is looking at this drug, currently on the market for children with lymphoblastic leukemia, as a potential treatment for adult leukemia and solid tumor cancers.

**Tasidotin** This tubulin-interactive agent is in Phase II trials for metastatic melanoma, non-small cell lung cancer, and prostate cancer.

**DENSPM** Genzyme accelerated its activity in small molecule approaches to oncology with a Phase I-II trial of this compound, which has demonstrated early activity in a variety of solid tumors. The company also plans to investigate the potential of the compound in liver cancer, an indication that has Orphan Drug status.

**DX-88** In partnership with Dyax, Genzyme is conducting a Phase III study of DX-88 for the treatment of hereditary angioedema (HAE), a life-threatening inflammatory condition that causes severe pain and swelling in the limbs, abdomen, and larynx.

**Tolevamer** Patient enrollment will continue in the Phase III study of this non-absorbed polymer therapy, which could be the first non-antibiotic treatment for *Clostridium difficile*-associated diarrhea.

**Synvisc 2 and Hylastan** Enrollment continues in trials of these potential next-generation viscosupplementation products for the treatment of osteoarthritis pain. Genzyme is predicting a US launch of Synvisc 2 in 2007, and a US launch of hylastan in 2008.

**Sevelamer** Clinical studies are underway for sevelamer carbonate tablets, a potential next-generation phosphate binder predicted to launch in 2008. Enrollment has been completed in a trial evaluating the product's equivalence to sevelamer hydrochloride for patients with end-stage renal disease. Genzyme also is evaluating the product for patients with chronic kidney disease, a significantly larger population.

help share the service costs associated with the category. And a competitor would presumably help shoulder the burden of treating patients who can't afford to pay.

But there has been real advantage for Genzyme in being the sole company to carry the weight of building infrastructure and awareness for the diseases it treats. And it is not clear what happens to its strategy for converting unpaid to paid patients if it is not the sole supplier of treatment in a given area. What is clear is that Genzyme will increasingly be faced with competitors. There are several reasons for that:

**Interest in orphans** "Because Genzyme has been so profitable on the basis of revenues from one drug," says Meyers from National Organization for Rare Diseases, "it's gotten a lot of other companies to say, 'Oh, maybe orphan drugs aren't so unimportant.'"

**Biogenics** In addition to branded competitors like Shire HGT, generic biologics pose a looming threat. In Europe, legal frame-

work exists for "biosimilars," as they are called there, which has allowed EMEA to move forward with draft guidelines on the topic. Final guidelines are expected in Europe sometime this year. FDA lags notably behind on creating such pathways, but says it will do so once Congress creates

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**SUSTAINABILITY MATTERS WHEN  
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CULTURE THAT PRODUCED THEM.**

the appropriate legislation.

**Pipeline products** Though the company remains committed to rare diseases, its pipeline has it moving into some more hotly contested areas, most notably, cancer, where a number of targeted therapies already exist. In December 2004, Genzyme laid down \$1 billion to acquire Ilex Oncology, a deal that delivered two marketable cancer treatments: Campath (alemtuzumab for injection), for treatment of B-cell chronic lymphocytic leukemia, and Clolar™ (clofarabine), for treatment of children with refractory or relapsed acute lymphoblastic leukemia. The company is currently looking at both drugs for additional cancer indications, and has several other cancer treatments in its pipeline (see “New Ground,” page 11).

A crowded space like oncology is uncharted waters for Genzyme, whose identity is centered on having first-to and only-in-market drugs. But the company says improving genetic knowledge of cancer (which is subdividing the category), combined with Genzyme’s experience in working with small patient populations, makes oncology a sensible next step.

Possibly. But with competing companies—many with several years of oncology experience—honing niche skills, Genzyme may have to rethink how it builds markets.

### Driving Ahead

With or without competition, Genzyme remains committed to serving Gaucher patients. Meeker points to a “long-standing program” on which Genzyme has spent over \$200 million trying to develop a gene therapy for cystic fibrosis. The program, as it relates to cystic fibrosis, “was not successful,” says Meeker, “but in the process, we learned a lot about different vectors and gene therapy.” This information could eventually lead to ways of more definitively addressing Gaucher disease.

One specific attempt at that is GENZ-112638, an oral, small-molecule therapy in development for Gaucher, which Genzyme says also has potential for treating other LSDs. Enrollment for a Phase II study of GENZ-112638 is expected to begin in the first quarter of this year.

“This would completely change life for Gaucher patients again,” says Meeker.

Indeed, National Gaucher Foundation’s Buyers says, “Delivery is an issue.” She says Gaucher patients would not be swayed by a new therapy, whether from Genzyme or a competitor, unless it was “at least as effective or more.” But she points out that biweekly infusions over a person’s lifetime are burdensome. “Obviously, if there was an easier way,” says Buyers, it’d be attractive.

The lesson a company learns by serving small markets of people whose very lives depend on continuous access to a product is that sustainability matters. For Genzyme, that means not just preserving access to these products, but also preserving the culture that produced them.

“How do we make sure it doesn’t disappear when we disappear?” That’s one of the questions that Termeer and the entire Genzyme organization is dedicated to answering on a daily basis, says Elliott Hillback, senior vice president of corporate affairs. Hillback has been with Genzyme since 1990, when Termeer recruited the fellow Baxter alum to head corporate

development. Today, he spends the majority of his time perpetuating the company’s culture, “so that ten years from now, this will still be as effective an organization,” he says.

One of Hillback’s main responsibilities is going out to business schools to give recruiting talks. His talks focus on the “importance of culture and how it ties into strategy,” he says. One of his resounding messages is that Genzyme thrives on flexibility. “If you want structure,” says Hillback, “don’t come here. Save yourself the energy.”

Hillback is not the speaker many MBA candidates expect when they sign up to hear about why a globally successful, technologically sophisticated biotech company values adaptability: He is a jolly, Santa Claus-looking (sans beard) character who seems more like a high-school basketball coach than a corporate executive. He’s round, with white hair, and wears red-plaid shirts and bifocals around his neck.

MBA’s also probably don’t expect Hillback’s method of explaining Genzyme’s philosophy: “If you’re an anal planner, you say, ‘I’m going to California. I’m going to get the AAA TripTik, and I’m going to take these roads, and here’s where I’m going to have breakfast, lunch, and dinner.’ Or if you’re really anal, ‘Here’s where I am going to go potty.’ And then, halfway through the first day, you listen to the radio, and it says there’s a huge blizzard in Chicago. And you say, ‘Well, my map says go through Chicago. I’m going to keep going.’”

Hillback pauses, and scans the room for some nodding heads amid mostly dumfounded looks from people wondering what this self-described “61 year old with the attention span of the 14 year old” is getting at. He bellows, “Duh! Come on gang! You’re not going to Chicago. Go to St. Louis. Go further south. Get to warm weather. Whatever you have to do.”

When Hillback, one of the first people I met at Genzyme, tells stories, his points seem obvious. (The company is smart in picking him to lure top talent.) But over the course of my visit, it became less and less apparent what the future holds for Genzyme. Built on the passion—and profits—found in helping long-ignored patient populations, Genzyme has grown into an envied empire. The test going forward, though, will be whether the company can uphold that reputation while maintaining its strategy of putting patients first. To do so, Genzyme must decide if it’s going to keep playing by its own rule book, or learn how to play by someone else’s.

Genzyme executives who found Theo Epstein’s resignation provocative may once again turn to the young baseball executive for a clue: On January 19, 2006, the Boston Red Sox unexpectedly announced that Epstein would rejoin the team as general manager. “Make no mistake,” said Epstein’s erstwhile mentor Larry Lucchino, in a statement: “Much work lies ahead for all of us, and we fully realize that our future conduct must conform to our sincere aspirations.”

You listening, Genzyme? 🗣️