

GENZYME: WHY DIVERSIFICATION IS STARTING TO LOOK SMART

As blockbusters become rarer and riskier, Genzyme's portfolio approach—grouping diverse business units selling a range of mid-sized products—looks increasingly smart.

BY MELANIE SENIOR

- Genzyme has historically traded a discount to its blockbuster-focused peers—mainly because of its multiple business units.
- But as the blockbuster model comes under threat, Genzyme's diversified approach looks particularly well-adapted to the current climate.
- Genzyme's focus on specialist areas and its tight customer relationships may help stave off the growing competition, while its history of growth through acquisitions means it's no stranger to external R&D.
- CEO and Chairman Henri Termeer's challenge today is to prove, through delivering on its growth promises, that Genzyme deserves an independent future.

Like most Big Biotechs, **Genzyme Corp.** has been associated with one major drug—its Gaucher's disease treatment imiglucerase (*Cerezyme*). With sales of more than \$1 billion—almost 30% of Genzyme's total revenues—the 13-year-old therapy is crucial to the company's economics.

But *Cerezyme* is still a lot less important to Genzyme than, for example, the EPO franchise is to **Amgen Inc.** or than interferon-beta-1a *Avonex* is to **Biogen Idec Inc.** The drug may be a blockbuster, but it's the outlier. Genzyme is a company of singles rather than home runs, insist its executives, pointing to the firm's dozen or more products besides *Cerezyme*, sold across a wide range of therapeutic areas.

Indeed, Genzyme's just as strongly associated with diversification and multiple business units as it is with *Cerezyme*—and it is on the basis of this spread-risk strategy that the company has delivered compounded earnings growth of more than 20% over the last five years and promises similar growth over the next five.

Sure, 20% doesn't dazzle alongside the boom years for biotech. Compared with Genzyme, "Amgen or Genentech may have enjoyed greater love and admiration [from Wall Street] because they have launched blockbusters that dominate entire areas and generate big numbers," suggests Stelios Papadopoulos, a former vice chairman of Cowen & Co.

Wall Street likes the simplicity of blockbuster stories. And many investors also like focus because they'd rather do their own portfolio management—creating a balanced market basket of rifle-shot investments of their own choosing—than have their biotech investments do it. The result is the diversification discount under which Genzyme shares have labored for more than two decades, notwithstanding management's attempt to address it during the '90s with the creation of tracking stocks allowing investment in specific business areas. (See sidebar, "The Tracking Stock Fiasco.")

Today, Genzyme's stock trades at a forward P/E ratio close to higher-flying competitors such as **Genentech Inc.** and **Gilead Sciences Inc.**, and significantly higher than Amgen. But that's got more to do with recent takeover speculation in Genzyme's stock (which rose 20% over the month of October 2007) and with Amgen's troubles, than with an appreciation of Genzyme's own strengths.

This may soon change, though. Thanks to pricing challenges, higher safety hurdles, and stiffer competition, blockbuster models are weaker than they ever

were. Amgen is struggling under a crumbling EPO franchise. (See “Can Amgen Find a New Engine?” IN VIVO, May 2007.) Biogen’s stock rocketed on the promise that acquisition could unlock additional value from its blockbuster-driven shares—only to fall again as even a desperate Big Pharma says it won’t overpay nearly to the extent investors had hoped. Against this backdrop, Genzyme’s diversification and reliable 20% growth begin to look pretty good.

Genzyme’s six, some very different, business areas, give it more choice of which auction to bid at in the increasingly competitive dealmaking market. (See Exhibit 1.) The biotech’s long-standing

Exhibit 1

Genzyme’s Business Areas

Rare Diseases (Lysosomal Storage Disorders)
Renal Disease
Orthopedics/Biosurgery
Transplant & Immune Disease
Oncology
Genetics & Diagnostics

SOURCE: Genzyme Corp.

embrace of external R&D—it has grown through nearly 30 acquisitions over the last 15 years—makes it more comfortable with the M&A process, and its aftermath, than peers that have only in

the last couple of years begun scrambling to externalize.

At the commercial end, Genzyme’s focus on orphan diseases found only among a handful of patients has compelled it to establish tight relationships with these customers, the specialists that prescribe the treatments, and the payors that fund them. These networks may help insulate it against growing competition: Genzyme is no longer alone in addressing rare diseases.

Nor, of course, it is alone as a dealmaker. But the company claims a leg up there, too—thanks to the global reach it has been forced to establish as it seeks out each and every rare disease patient, whatever their location. That, argues management, means it can assess the full global value of an asset, for example, as it did in the case of AnorMed’s transplant drug plerixafor (*Mozobil*), allowing it to justify out-bidding **Millennium Pharmaceuticals Inc.** for ownership of that company. (See “Genzyme Breaks a Biotech Taboo: The Hostile Bid for AnorMED,” IN VIVO, November 2006.)

Genzyme’s complex structure takes rather more effort for analysts and investors to follow than straightforward biotech. The divisions are run quasi-autonomously, with CEO and president Henri Termeer as overseer—in a sense playing the portfolio manager role that many investors see as theirs, not the CEO’s. That may be why activist investor Carl Icahn recently took a sub-1% stake in Genzyme—perhaps with an eye to breaking up the company and selling its specialized parts for more than they contribute to Genzyme as a whole.

But Genzyme isn’t about maximizing shareholder value at any one specific point in time. It’s about growth over the long term; growth that rewards long-standing shareholders by building a stable company. More importantly, its leaders believe that

corporate-driven portfolio management, particularly in niche businesses, ultimately drives more stable, faster, and higher-profit growth by taking advantage of development, commercial, and customer commonalities.

And when it comes to growth in the pharmaceutical industry, small is surely the new big—even the centralized Big Pharma are seeking to create leaner, more creative biotech-like units, albeit for now mainly within their giant R&D organizations. Likewise, specialist drugs are the new primary care. So as the blockbuster model comes under threat, Genzyme may find its own version starts to earn a bit more love—granted it continues to prove that it can turn theoretical advantages into real growth.

UNDER THREAT, OR MISUNDERSTOOD?

It still has some convincing to do, at least on Wall Street. Most analysts believe that Genzyme can deliver its promised 20% earnings growth over the next two or three years. The doubts set in after that—largely because of forecast competition in the rare disease franchise that still accounts for more than a third of revenues.

The bears point to potential 2009 competition for *Cerezyme*, for now the only enzyme replacement therapy in Gaucher’s, from **Protalix BioTherapeutics Ltd.**’s Phase III recombinant, plant-cell-based glucocerebrosidase (prGCB), which the company claims may be more effective and have a longer half-life than *Cerezyme*. **Shire PLC**’s human equivalent, gene-activated glucocerebrosidase (GA-GCB), may be on the market a year later. Beyond that, **Amicus Therapeutics Inc.**’s two Phase II oral candidates for Gaucher’s and Fabry’s disease could present a whole new treatment paradigm in these areas—and the threat got bigger in November 2007 when Shire threw its resource and expertise around ex-US rights to these plus a Phase I Pompe’s disease asset.

Skeptics also question the growth potential of some of Genzyme’s late-stage hopefuls—and the price paid for them. *Mozobil* was the prize from Genzyme’s \$600 million AnorMed buy, but some analysts forecast sales of just \$100 to \$200 million—half of Genzyme’s \$400 million forecast. The product increases the number of stem cells collected prior to the stem cell transplants used in hematological malignancies and is expected on the market next year. But some are unclear on precisely how many patients would qualify, what the long-term outcomes might be, and whether the product will be fully reimbursed (many stem cell transplant procedures are only partially funded).

In Genzyme’s renal franchise, the company’s second biggest drug, phosphate-binder sevelamer (*Renagel*), is maturing and critics see its follow-on replacement, *Renvela*, as poorly differentiated, particularly in contrast to Amgen, which, through its recent acquisition of Ilypsa, now has a Phase III phosphate-binding polymer that may be more potent than *Renagel*. In **Genzyme’s Biosurgery** division, hylan G-F 20 (*Synvisc*), a visco-supplement used to treat pain associated with osteoarthritis of the knee, hasn’t grown as fast, nor proved as competitive, as expected, say some—and a simpler, single-injection form of the treatment, *Synvisc-One*, just got delayed pending additional data.

There are also murmurs over the quality of Genzyme’s earnings—though it’s hardly alone in cutting SG&A costs, and the

3%, inflation-linked price increases to its lysosomal storage disease (LSD) drugs, like *Cerezyme*, isn't unusual either. Still, "although we can't fault the growth track record," says Phil Nadeau, managing director and senior research analyst at Cowen & Co., "on the long-term we're skeptics," he says, with forecasts below the company's guidance, mostly because of individual product sales predictions and the impact of competition. Adds Bear Stearns analyst Mark Schoenebaum: "The 2010 to 2015 period is what people are worried about."

THE VIRTUES OF LEVERAGE

That's because people don't understand Genzyme's business model, says the company's EVP, legal and corporate development Peter Wirth. The Street, he says, focuses on individual products and misses what's "really driving our growth." Genzyme, he argues, is a whole lot more than the sum of its individual drugs. Its global franchises, international infrastructure, high degree of vertical integration, and its position in the specialist health care community offer unrivalled leverage opportunities, both in finding and growing new products, and from the authority and credibility Genzyme claims that it now commands among payors and governments.

The expansion of Genzyme's rare genetic diseases franchise illustrates that leverage. Since the launch of plasma-derived glucocerebrosidase *Ceredase* in 1991 and its recombinant equivalent *Cerezyme* three years later, the company has added three further lysosomal storage disease drugs: agalsidase beta (*Fabrazyme*) for Fabry's disease, laronidase (*Aldurazyme*) for mucopolysaccharidosis I (MPS I), and most recently, alglucosidase alfa (*Myozyme*) for Pompe's disease. Together, these products are on track to sell more than \$2 billion this year—in the context of overall projected revenues of about \$3.7 billion.

There are some obvious areas of overlap—distribution and manufacturing, for instance. All four drugs are made at the same plant (although *Myozyme* needs a new factory of its own because volumes are so big). But since its early experience with *Ceredase* and *Cerezyme*, Genzyme has learned how to more effectively identify and track patients with rare diseases, it has more and better tailored infrastructure to do so, it knows the best ways to partner with doctors, and it has established relationships with payors and governments that apply across all four drugs. This experience may help explain why *Myozyme* has gotten off to such an unexpectedly strong start since its launch in the spring of 2006. Cowen's Nadeau reckons 2010 sales could reach \$500 million.

Genzyme also learned, in Gaucher's, how to set up global patient registries to track patients' treatment response and disease

progression, and "we're translated that knowledge into similar registries for our other drugs," notes Geoff McDonough, SVP, lysosomal storage disorders business unit. And that registry data in turn help address payors' growing demands for proof of value—which is otherwise difficult to do with just a handful of patients.

Indeed, although Gaucher's affects only a few thousand patients worldwide (*Cerezyme* treats about 4,500) and Fabry's disease even fewer, the value-hurdles are hitting here, too—these are some of the most expensive drugs around. *Cerezyme* can cost up to \$250,000 per year. Most Western countries reimburse enzyme replacement therapies, but eligibility and outcome criteria are getting tougher. The challenges of assembling outcomes data prior to approval has prompted schemes such as that in the

SHIRE STEPS UP PRESSURE ON GENZYME

In another sign of the value of ultra-specialist drugs for niche diseases, Shire beat several competitors to win ex-US rights to Amicus' Phase II Fabry's and Gaucher's candidates, and its Phase I Pompe's disease program. The financials: \$50 million up front and up to \$150 million in milestones through approvals, shared development costs from now on, and tiered double-digit royalties on all three compounds. Considering these are rare, inherited disorders that affect only a few thousand patients worldwide, and that this is a regional deal, the money's not bad. All the more so because lead compound migalastat (*Amigal*) in Fabry's hasn't even reached proof-of-concept yet, although Shire was probably offered access during its due diligence to more of the ongoing Phase II data than the rest of us.

Shire was already brushing shoulders with Genzyme; directly in Fabry's disease, where it sells a competitor to Genzyme's *Fabrazyme* in Europe, and indirectly via Shire's ownership of the only enzyme replacement therapy for Hunter's syndrome, *Elaprase*. In renal disease, Shire's *Fosrenol* is also a head-on competitor to Genzyme's *Renagel*.

Since its deal with Amicus, Shire has become a more formidable threat—at least to Genzyme's rare diseases franchise. Now sure, even Shire acknowledges that oral therapies likely won't replace enzyme replacement therapy entirely because they don't work equally well in all patients. But there's no doubt that the cosy exclusivity that Genzyme has enjoyed since first creating this business—helped along by orphan drug status for its drugs—is coming to an end. Others besides Shire are waiting in the wings, too—like Targeted Cell Therapies, for instance, with a preclinical, orally administered gene-delivery approach.

Genzyme's hold will be tough to crack. But as Shire in particular gains more product candidates in rare diseases—adding to its own, near-term enzyme replacement therapy that will compete with *Cerezyme*—it increases its own visibility, credibility, network, and leverage opportunities in this specialist niche.

Netherlands, where the government has agreed to provide new treatments for rare diseases—including *Myozyme*—over three years while prospective outcomes data are collected.

RELATIONSHIPS AS COMPETITIVE DEFENSE?

In markets like China or Egypt where there's no reimbursement, Genzyme funds the drug itself for those who need it—currently about 600 patients globally. In some countries, such as Malaysia or Venezuela, governments have gradually developed the means to pay, or part-pay, for the treatments. Still, the credibility that Genzyme feels it gains as a result of this patient support is another key—if intangible—aspect of the business model, says Wirth: "If

patients are on our side, demanding access to therapies . . . then we have a powerful way of dealing with the rest of the world.”

Including competitors. In the small, tight-knit community of patients, physicians, and patient advocates in rare genetic diseases, it may be hard for newcomers to break in without clearly superior efficacy. Genzyme expects most of the competitor impact to come around new patients. “I can’t think of a single instance of where a patient who is well-controlled [on an existing therapy] would be changed to another drug,” opines Wirth. Because of the support structure, he adds, “they’re not neutral about where they get their therapy.”

A big price differential might sway them, though. Physicians polled by Cowen analysts reckon it would have to be at least 25% for new entrants to take any meaningful share. That may not be affordable for newcomers. And besides, notes McDonough, if necessary, “we’d be able to make that [potential price] gap less meaningful”—presumably by cutting Genzyme’s own price.

It may not have to, if the Fabry’s disease market is anything to go by. In 2001, European regulators somewhat unusually granted co-orphan exclusivity to both *Fabrazyme* and Shire’s agalsidase alfa (*Replagal*). In this case, a price battle would have been in neither party’s interest, and there wasn’t one (though granted, a competitor arriving much later might have more incentive to compete on price). Both Fabry’s disease drugs cost about the same, on an average annual basis—although, somewhat confusingly, the required dosage is much higher for *Fabrazyme*. **Shire Human Genetic Therapies Inc.** president Sylvie Gregoire wouldn’t comment on future pricing for Shire’s future Gaucher’s treatment GA-GCB, but she suggested that the drug’s human derivation might offer some advantages over *Cerezyme*.

A small-molecule drug for Gaucher’s or Fabry’s disease could shake up market dynamics a lot more, however. *Cerezyme* and

Fabrazyme work well in a majority of patients, but a fortnightly infusion isn’t much fun. Amicus’ pharmacological chaperone treatments migalastat (*Amigal*) and isofagomine (*Plicera*), for Fabry’s and Gaucher’s disease, respectively, could take a significant share of these limited markets—if they work. Pharmacological chaperones are small chemicals that help correct or at least mitigate the protein misfolding that triggers the build up of lysosomal substrate—the key pathology of these lysosomal storage diseases. “They’re addressing the underlying cause of the problem,” explains Amicus’ CEO and president John Crowley. And Shire validated his optimism by paying a \$50 million up-front fee for ex-US rights to the programs even before full Phase II data were available. (See sidebar, “*Shire Steps Up Pressure on Genzyme.*”) Amicus’ therapies aren’t likely to be small-molecule-style cheap, but they could be a good bit cheaper than the enzyme replacement therapies.

Genzyme is pursuing its own oral therapy for Gaucher’s, which it claims could be on the market in the next three to four years, ahead of Amicus’ candidate. GENZ 112638 works by inhibiting substrate synthesis. That’s the same basic mechanism of action as **Actelion Ltd.**’s marketed miglustat (*Zavesca*), which validates the pathway, notes McDonough. Unlike chaperones, which may only be useful for a subset of patients (albeit a majority subset in Gaucher’s and more than half in Fabry’s, according to Crowley), Genzyme’s candidate could potentially treat all Gaucher’s patients. Now granted, *Zavesca* hasn’t taken much market share from the enzyme replacement therapies—it’s approved in Europe only for those who can’t tolerate ERT. But because Genzyme’s candidate is a far more specific enzyme inhibitor than *Zavesca*, it hasn’t shown the same side effects either, argues McDonough.

Still, until the Shire-Amicus deal, Genzyme had a safety net in case its oral program stumbled: buying Amicus. With half the program’s value partnered with a head-on competitor, that option looks less plausible.

Exhibit 2a

Genzyme Tops Big Biotech M&A Ranks (by number of deals)

COMPANY	NUMBER OF ACQUISITIONS SINCE 1991 (TOTAL VALUE)
Genzyme	29 (\$5.9 billion)
Amgen	8 (\$22.8 billion)
Gilead	5 (\$3.7 billion)
Millennium	4 (\$2.5 billion)
Biogen Idec	4 (\$7 billion)*
Celgene	3 (\$2.9 billion)
Genentech	1 (\$905 million)

*Includes Biogen-Idec merger in 2003. All figures exclude earn-outs.

SOURCE: Windhover’s *Strategic Transactions Database*

Exhibit 2b

Genzyme Acquisitions Since 2000 (up-front deal value \$mm)

2007	Bioenvision (345)
2006	AnorMed (584)
2005	Bone Care International (600)
2005	Verigen (10)
2004	ImPath (215)
2004	Ilex (1015)
2003	SangStat Medical (596)
2001	Novazyme (137.5)
2001	Wyntek Diagnostics (65)
2001	Focal (9)
2001	Lisfarma (n/a)
2000	GelTex (1000)
2000	Biomatrix (851)

SOURCE: Windhover’s *Strategic Transactions Database*

BUYING BEYOND RARE DISEASES

Not that Amicus' Crowley has—or had—any plans for the company to be acquired. For Genzyme, though, acquisitions are part of its culture. “While other Big Biotechs were trying to show how robust they were on their own, Genzyme capitalized on the industry’s broader output,” notes Papadopoulos.

The result, according to Termeer, is that buying external programs “is a natural way for us. We know what integrating different cultures means, and how to run a number of different operations.” According to Papadopoulos, Genzyme views acquisitions “in the context of operating decisions, rather than agonizing over them as major strategic events,” as do some biotechs. Genzyme has completed almost 30 acquisitions since the early 1990s compared with just eight for Amgen and four for Biogen. (See Exhibits 2a & 2b.)

Not all of those deals worked out. Deknatel and its postsurgical adhesion products wasn't in the end worth \$250 million; nor was ImPath's cancer diagnostics business worth the price Genzyme paid in 2004. The jury's still out on more recent deals including Bone Care International and AnorMed.

But a number of Genzyme's deals certainly have worked out spectacularly. One of its earliest—the 1989 acquisition of Integrated Genetics—brought Genzyme the capability (and the plant) to create *Cerezyme* (until then it had no recombinant technology capabilities). IG's CEO, Robert Carpenter, is still on Genzyme's board and its research VP, Alan Smith, PhD, is now SVP in charge of Genzyme's research. More recently, the 2000 acquisition of GelTex brought *Renagel* and Genzyme's most significant expansion beyond rare diseases—the renal franchise accounts for almost a fifth of revenues. (See Exhibit 3.) Launched in 1998, *Renagel* is recognized as the best and safest treatment for hyperphosphatemia (elevated phosphorus levels) in dialysis patients, with a 50% market share in the US. Sure, it's maturing. But the drug is beating Shire's lanthanum carbonate (*Fosrenol*) hands down—at least on that side of the pond. *Fosrenol*, introduced in 2005, was positioned as more convenient and efficacious than other phosphate binders, but it suffers from lingering safety concerns around the effects of metal absorption. Its US market share is less than 10%.

Meanwhile, Genzyme is counting on two further drugs to shore up its presence as a renal care player, one from outside, one from inside. *Hectorol*, a pro-Vitamin D analog for hyperparathyroidism, came with the \$600 million purchase of Bone Care International in 2005—an example of how leverage is

possible between business areas, as well as within. “Tactically, this [acquisition] was to gain a product that's used in dialysis patients” and thus to slot in alongside *Renagel*, explains John Butler, president of Genzyme Renal. Strategically, though, it was a way for Genzyme to access chronic kidney disease (CKD) specialists—because unlike *Renagel*, *Hectorol* is approved for both dialysis patients and for the far larger CKD population. The CKD market is, likewise, the one that Genzyme wants to reach with *Renvela*.

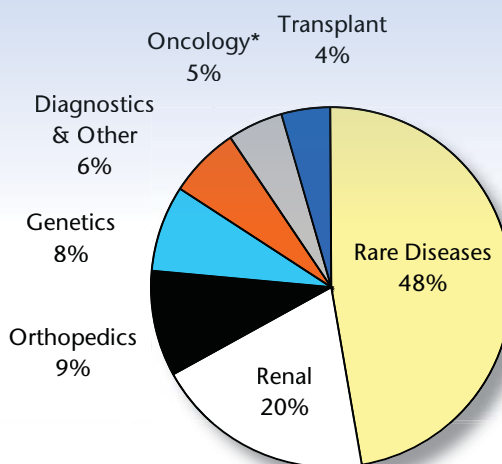
Renvela isn't much different than *Renagel*. But it does shore up bicarbonate levels—which can drop with *Renagel* use—and reduces the gastrointestinal side effects associated with *Renagel*, according to management. And although Butler acknowledges that bicarbonate levels “are not a clinical concern,” since they can be corrected during dialysis, he argues that this plus the GI profile may be enough to promote earlier use of *Renvela* among CKD patients. “Most patients are on [cheaper] calcium [-based binders] when they start dialysis, and there has to be some traumatic event before they'd change treatment” onto *Renagel*, he explains. Genzyme hopes to persuade nephrologists, with clinical data, that early use of *Renvela* in pre-dialysis patients can simplify treatment and prevent the need to switch treatments at all once a patient moves onto dialysis.

It's not yet clear what data Genzyme will need to persuade the regulators, however (some docs already use *Renagel* off-label in CKD). Although an FDA committee recently voted to extend the use of phosphate binders into pre-dialysis patients with elevated phosphorus, they didn't agree on what markers might be used to prove that earlier benefit. So initially at least, only those patients with GI toxicity problems or high bicarbonate levels will go onto *Renvela*. “We're not out to change all *Renagel* patients onto *Renvela*,” notes Butler—not yet, anyway. For now it's about expanding the sevelamer franchise, he continues.

But the uncertainties over CKD data requirements and Genzyme's recent failure to get *Renvela* approved as a more convenient once-a-day powder help explain analysts' lack of conviction. Certainly the regulatory wind is blowing against poorly differentiated follow-ons. Yet Butler remains confident that *Renvela* is part of the answer to protecting the *Renagel* franchise, including from Amgen's AMG 223 (the Ilypsa compound), which could reach the market by 2010. *Renagel*'s own leading position was established gradually, Butler recalls, as the drug's added benefits were proven in outcomes trials comparing *Renagel* with

Exhibit 3

Business Unit Share of 2007 Revenue Based on FY estimates



*includes Thyrogen

SOURCE: Genzyme Q3 2007 earnings; Company and analyst reports

calcium-based phosphate binders among hemodialysis patients. As such, “we’ve done this before,” Butler argues. *Renvela* aside, Butler claims that the breadth of Genzyme’s offerings in renal disease is second to none—besides the renal franchise drugs, *Fabrazyme* addresses the renal disease component of Fabry’s disease, and anti-thymocyte globulin (*Thymoglobulin*) is sold for acute renal graft rejection. He doesn’t rule out future acquisitions to broaden the franchise further. “We’re always looking externally for opportunities,” Butler says.

VALUE IN SMALL, COMPETING, GLOBAL UNITS

Butler knows he’s up against competing priorities from other business unit heads, though. Each of Genzyme’s divisions is run quasi-autonomously by leaders who are at least partly

Pharmaceutical Inc.’s Phase III mipomersen for a rare genetic cardiovascular disease called familial hypercholesterolemia. But that’s fine, says Butler; it just means “I’ll find other ways to deliver my bottom line,” such as cutting out a higher-risk program, or one with lesser commercial potential. In other words, Butler and his counterparts are forced to better prioritize and to manage costs most effectively.

Now granted, the Genzyme setup “makes for reasonably complicated management,” acknowledges Butler. Executives in the research and development organizations, for instance, report along functional lines to SVP, research and CSO Alan Smith, or, in development, to CMO Richard Moscicki, MD. Yet within those groups are those who remain closely aligned with the interests of each of the business units. Where business

development’s concerned, each unit’s slightly different: some, like oncology, have their own dedicated team reporting through the business unit; in others, including rare genetic diseases and transplant, business development is managed out of the corporate group.

Still, this doesn’t stop Genzyme from reaping the benefits that its small units give it in dealing with partners, says Wirth. From the outside, “we’re pretty transparent,” he argues. Smaller organizations are easier for potential partners to approach and deal with. Rather than navigating layers of bureaucracy and finding the right person, each partner knows that the head of the unit is responsible for business development, too—and will be for the long term. “I have to understand what I put in front of Termeer and that I can deliver on it,” illustrates Butler. It’s not like being a BD person in a Big Pharma who then moves onto the next project, leaving the follow-up job to alliance managers or someone else.

Thus negotiations with AnorMed were championed by Joe Lobacki, SVP, transplant business unit, supported by a corporate business development team. “Lobacki was able to convince AnorMed’s management that he was the person with direct personal responsibility as head of transplant,” notes Wirth. As is increasingly the case, initial licensing negotiations (around *Mozobil*) turned into acquisition talk; less typically, however, one of AnorMed’s major investors, Baker Brothers Advisors, rebelled. Rejecting Genzyme’s offer as too cheap, they seized control of the board and ultimately forced Genzyme to go hostile. When Millennium joined the bidding, too, Genzyme had to up its price—to \$600 million, 58% above its initial offer.

But although some analysts feel that Genzyme paid too much for the product, Genzyme saw the deal as a demonstration of its ability to leverage its global infrastructure. “We could evaluate the deal in a way that Millennium couldn’t,” says Wirth, because Millennium doesn’t have the global reach that Genzyme does—achieved, in transplant, largely through the \$596 million acquisition of SangStat Medical in 2003.

It was the rare diseases focus that forced a global mentality on Genzyme from the start, though. If a drug can help on just a

THE TRACKING STOCK FIASCO

Genzyme’s management in the late 1990s tried to mitigate the diversification discount by creating a handful of tracking stocks—shares in separately listed but wholly owned divisions of the company. The theory: raise money for the various growing divisions—including tissue repair, surgical products, and molecular oncology—without diluting the parent shares of Genzyme general. Diversify without affecting the core business P&L, in other words, with the added benefit of incentivizing business unit employees with divisional stock (and saving some tax). (See “Keeping Track of Genzyme,” *IN VIVO*, October 1997.)

It didn’t work. The tracking stocks were soundly rejected as financial window-dressing at a time of tremendous skepticism around novel financial vehicles (remember **Elan Corp PLC?**). Then the biotech bubble burst at the turn of the decade and investors weren’t interested in investing in small, risky individual units anyway.

So Genzyme won’t be trying that again—and nor, argues EVP, legal and corporate development Peter Wirth, does it need to. “We can do much more within our own P&L now.”

compensated based on their unit’s performance. They have P&L control and are responsible for day-to-day activities; they present business development proposals to the CEO and other managers. Each competes for business development and R&D resource from a central pot.

According to Butler, the end result is a highly entrepreneurial environment where “we get the best of both worlds.” A degree of competition between the business units forces better decision-making and prioritization, yet at the same time, everyone’s singing from the same corporate hymn sheet. Thus although “my job is to advocate for the renal business” in the budget and business development processes, notes Butler, “I’m also an officer of the company.” All team heads consider the various priorities for growing the business as a corporate whole, even if they’re not in his or her area.

Right now, for example, the renal business isn’t getting a lot of extra resources. *Mozobil* and alemtuzumab (*Campath*), in Phase II for multiple sclerosis, are the top development priorities, sucking up a big chunk of the development budget. On the business development front, Genzyme is also reportedly interested in *Isis*

few patients, these patients have to be found, wherever they are. As such, we “never thought of the world in terms of ‘US and the rest’,” says Wirth. Today, more than half of Genzyme’s revenues are outside the US; its third largest country market is Brazil. Asian strength allowed Genzyme to grab at least some territory rights to Shire’s Hunter’s syndrome drug idursulfase (*Elaprase*)—even if overall this remains one storage disorder drug that got away, from Genzyme’s perspective. Internationalization continues: Genzyme just received reimbursement for its LSD drugs in Russia, and has expansion plans in China and India, too.

R&D: RISKY, BUT OPEN-MINDED

Genzyme global isn’t just about sales offices, though; it’s also about R&D. The company recently signed a rare diseases collaboration with ViaCruz, the Brazilian equivalent of the US’ NIH, and last month it announced a joint venture in China on its Parkinson’s candidate with gene therapy play **Sunway Biotech Co. Ltd.**, which already has a marketed gene therapy on the Chinese market. (See “*The Chinese Gene Therapy Hotspot*,” The In Vivo Blog, October 26, 2007.) “If you’re going to be present, you need to be part of the community,” emphasizes Wirth, echoing similar views among Big Pharma and some biotechs as they build their presence in the developing world. (See “*Novartis Buys into New Pharma World Order*,” IN VIVO, December 2005.)

Genzyme’s management claims that the company’s expertise in unproven, and thus riskier areas such as gene or cell therapy give it another advantage in the competitive dealmaking world. “We can consider areas that others might find challenging, like gene therapy,” notes Wirth, pointing to a June 2007 licensing deal with **Ceregene Inc.** for ex-US rights to a Phase II Parkinson’s candidate. This November, Genzyme agreed to collaborate with France’s **Fovea Pharmaceuticals SA** on finding gene-related therapies for retinal dystrophies, including rare inherited ones.

Is a presence in gene therapy a competitive advantage, though, or just being where most others don’t want to be, even if they could? The majority of Big Pharma bailed out on gene therapy during the ‘90s following some high-profile clinical accidents, and although there are signs that interest is returning, this isn’t exactly a technology hot-spot. (See “*Gene Therapy: The Next Big Thing?*” START-UP, October 2007.) Genzyme, though, has stuck with it—“I’m surprised so many stepped back,” says Termeer—and now has two clinical gene therapy programs, in Parkinson’s and peripheral arterial disease, and more behind.

“We’re not afraid of new technologies,” Termeer continues; nor indeed of risky ones. Some of Genzyme’s efforts have stumbled, such as early work in cancer immunotherapy, and the company’s polymer therapy, tolevamer, which this year failed its Phase III trial in *Clostridium difficile*-associated diarrhea. But Genzyme’s broad and diversified business model arguably permits it to take technology risks further upstream. And that’s its duty, argues Termeer. “We must continue to innovate and ensure we do the most in terms of servicing patients. Copying is not our model; it’s the new stuff that’s sustainable.” Overall R&D spend looks set to remain at 17% of revenues; that’s several percentage points below other Big Biotechs like Amgen or Genentech, but only a shade below the industry average, according to Steven Silver, biotech

analyst at Standard & Poor’s.

In part because of gene therapy’s risk profile, and in part because of past failures, investors don’t think much of Genzyme’s R&D outside rare diseases. “It’s B grade,” says one analyst. But Genzyme doesn’t make much of a distinction between internal and external R&D—and there’s no question its external R&D has been highly productive (development-stage *Renagel*, for example, was part of a joint venture with GelTex Pharmaceuticals Inc. before it was wholly acquired). Now it’s working on a wide range of indications for *Mozobil* beyond autologous transplants, including in chemosensitization. Indeed, although “Genzyme may not have excelled in discovery, it does make something of compounds that it acquires,” opines Papadopoulos.

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Stelios Papadopoulos
Former vice-chairman
Cowen & Co.

One gem that might shine up quite nicely is monoclonal antibody alemtuzumab, which came with the acquisition of Ilex Oncology in 2004. The compound is already marketed by **Bayer Schering Pharma AG** as *Campath* for chronic lymphocytic leukemia. But Genzyme and Bayer are looking at the drug’s potential in multiple sclerosis, and released Phase II results from a two-year study earlier this year showing a significant reduction in the frequency of relapses and improvement in accumulation of disability relative to **Merck Serono SA**’s interferon-1a (*Rebif*)—which is already shown to reduce relapses by 30% or so. If the data are replicated in later trials, bullish analysts including Bear Stearns’ Schoenebaum say the drug—which would be the most effective on the market, with potential to restore function—could reach \$500 million or even \$1 billion.

One big problem: *Campath*’s class association with Biogen Idec’s natalizumab (*Tysabri*), which was withdrawn from the MS market in early 2005 following three cases of a rare viral infection in the brain, two of which were fatal. It was later reintroduced, but with significant restrictions. The alemtuzumab trial was temporarily suspended in 2005 due to three cases of immune thrombocytopenic purpura (low platelet count), one fatal. Given FDA’s highly cautious stance these days, alemtuzumab in MS is a long shot, opines Cowen’s Nadeau.

It may also pose a pricing challenge. The amount of *Campath* required for MS is far less than the amount needed for treating CLL. Re-pricing the drug could prove difficult, given the issues Genentech has faced with AMD treatment ranibizumab (*Lucentis*), which is a variation of cancer treatment bevacizumab (*Avastin*), yet is many times more expensive on a per-dose basis. (See “An

Eye for an Eye: Lucentis and the New Pharmaceutical Value System,” The RPM Report, June 2007.) So *Campath* may forcibly become one of the lowest-cost antibodies on the market—good for payors, certainly, but less attractive for Genzyme’s bottom line.

TOMORROW’S GROWTH

If it does work, *Campath* will help Genzyme in its mission to diversify from its core in rare and renal diseases into new areas. Meantime, though, Genzyme’s having to adapt its broader acquire-to-diversify approach to a changing dealmaking environment.

Until now, the company has sought to establish a commercial presence in areas where it has a research interest, before investing significant R&D dollars. This prudent, rather specialty-pharma-like strategy has worked fine up until recently, and in part explains the company’s reputation among some observers as buyer of “cheap and mature” businesses.

Buying cheap, established firms may now be a tougher prospect, as Genzyme’s recent acquisition of Bioenvision suggests. Bioenvision had been Genzyme’s EU marketing partner for acute lymphoblastic leukemia drug clofarabine (*Clolar*), sold in Europe as *Evoltra*. It also sells breast cancer drug trilostane (*Modrenal*) in the UK. This deal was delayed by several months by an activist shareholder who felt Genzyme’s offer of \$5.60 per share was too low. Genzyme won in the end, though, thereby shoring up its commercial presence in oncology. But it has more work to do. “We’d like another company like Bioenvision,” says Wirth, to add scale in oncology, and “we’re actively looking for opportunities to establish a commercial presence in other areas” like immunology, fibrotic diseases, and neurology, where Genzyme has research activities but not much downstream.

Genzyme’s breadth means it has a choice of areas where it can compete for opportunities at any given time, and its decentralized structure may make it easier to enter new ones. But even so, the company has had to adapt its business development philosophy and, in particular, to consider earlier-stage transactions. “Typically we’d target marketed products,” says Wirth, but “in the future we’ll look at opportunities with compelling Phase II data and some development risk,” he says. AnorMed with its Phase II compound is an early example.

THE TOUGHEST TEST?

Competing for Phase II compounds won’t be a piece of cake either—proof-of-concept drives much of today’s dealmaking. In a sense, then, Genzyme now faces one of the toughest tests of its business model. The theoretical advantages of a multi-unit, specialist approach with tight customer/payor relationships have become clearer. But leveraging these advantages to create real growth is harder. Plenty of others are now pursuing rare diseases—think of Amicus, Shire, **Alexion Pharmaceuticals Inc.**, or **BioMarin Pharmaceutical Inc.** (The US and European regulators just made orphan drug applications easier, too, encouraging further work in rare diseases.) Oncology is crowded, and it presents unique challenges for drug developers (see “Phase III Prostate Cancer Failures: *Taxotere to Blame?*,” in this issue). Everyone’s going specialist, too, even Big Pharma.

Still, while acquisition rumors swirl around the ranks of other Big Biotech—most notably Biogen Idec, which put itself up for sale in October—Termeer seems determined to remain independent. (See “*The Biogen-Idec Sale: It’s About Revenues, Not Biologics,*” The In Vivo Blog, October 17, 2007.) “It was quite deliberate from the start,” he tells *IN VIVO*, “to be diversified, global, and independent.” The company chose its programs in line with those goals, and it has made a point of being as vertically integrated as possible. Biogen’s purer, blockbuster-focused model means it “never really diversified in the way we did from the beginning. That makes you vulnerable at some point,” says Termeer—not least to activist shareholders such as Carl Icahn.

So Genzyme’s a less obvious target for Big Pharma, according to Termeer and other observers. Its multiple units “would not be the easiest to incorporate,” notes Papadopoulos. Leverage and cost-savings would be hard to come by, and Big Pharma likely wouldn’t find Genzyme’s variety of niche and often complex drugs particularly useful *Band-Aids* for their pipeline problems. (See “*Why Genzyme’s Unlikely to be the Next Target,*” The In Vivo Blog, November 16, 2007.)

Any potential acquirer would also have Termeer himself to contend with. Unlike Biogen’s CEO Jim Mullen, who joined the company long after it had become one of the industry’s biggest successes, Termeer joined Genzyme as CEO very near its beginning. Termeer isn’t Genzyme, but he’s at least as closely identified with his company as any CEO—probably more so. No CEO has run a major biotechnology company as long as Termeer has run Genzyme. Moreover, note his associates, Genzyme is a platform for the leadership roles Termeer plays in the industry and in a variety of nonprofit institutions—roles he clearly relishes. Termeer can’t sell Genzyme without letting go of an important part of himself.

Termeer says he knows that “we have to earn our independence, every day, by doing good things for all our constituents,”—including shareholders. He told *IN VIVO* shortly before the news emerged of Icahn’s stake in Genzyme that he wasn’t aware of any activists in the stock. But he certainly doesn’t dismiss them, either. “They’re a good thing in one sense,” he says, “since they force management to understand where their vulnerabilities are, and to unlock maximum value from the business.”

Just you try, Icahn, in other words.

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