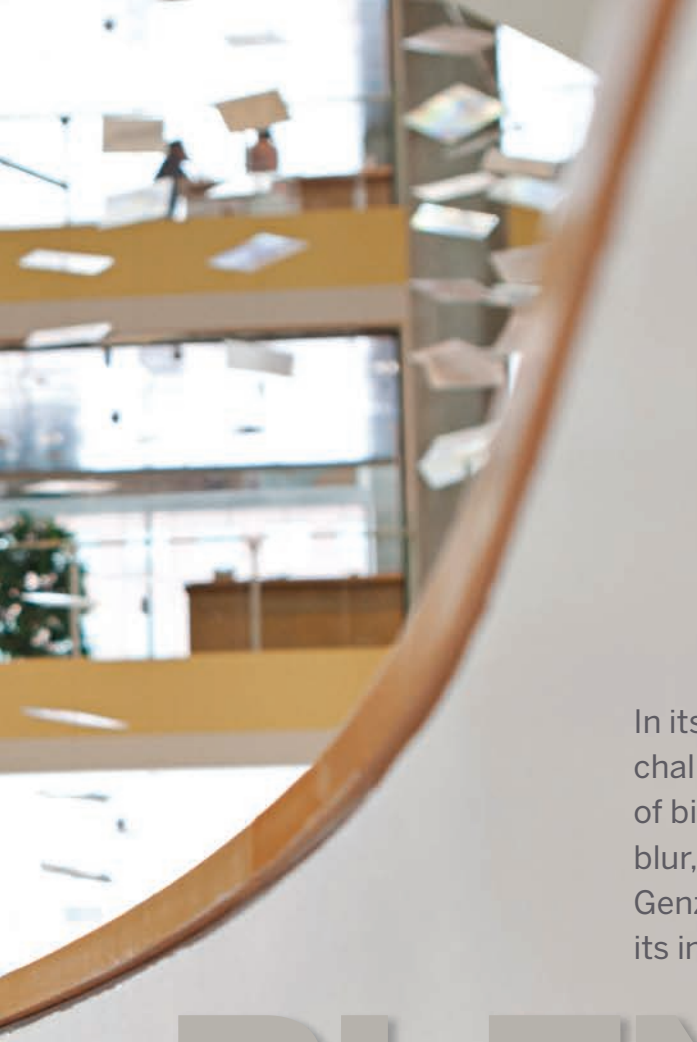
Bill Sibold, SVP, head of MS for Sanofi's Genzyme unit



In its quest for acquisitions to ease productivity challenges, pharma has sought to co-opt the tools of biotech. It's not always successful. As the lines blur, and traditional distinctions lose their relevance, Genzyme's Bill Sibold shows how biotech can retain its innovative edge. **Marc Iskowitz** reports

BLENDED BIOTECH

Genzyme opened its doors in inner-city Boston in 1981, five years after Genentech birthed the biotech industry on the opposite coast. Its enzyme-replacement injections, like Ceredase for Gaucher disease and Fabrazyme for Fabry disease, would go on to become commercial hits and the company a leading light in the rare-disease treatment space.

But after Paris-based Sanofi purchased Genzyme in 2011 for $20.1 billion, the biotech would become known for more than needle-based therapies. Sanofi had acquired rights to the MS pill Aubagio when it snapped up Aventis in 2004. And Genzyme was developing Lemtrada, an MS biologic which was a centerpiece of the sale.

Today, the commercial launches of both MS drugs are being led out of Genzyme's head office in Cambridge, MA. The arrangement doesn't seem to fit neatly into the classic definition of a biotech firm: one that commercializes only scientific tools developed by molecular biologists. Actually, "[Few] companies take a pure-play, 'We-are-only-a-biologic-or-small-molecule-company,' approach," says Bill Sibold, SVP, head of MS for Genzyme. To Sibold, it's perfectly natural for a biotech to be selling a pill. After all, specialty is specialty, no matter the product's formulation. "If you're focused on science and patients…it really doesn't matter."

Sanofi's decision to put pill and biologic under the smaller company is another example of the biotech-

PHOTO: BILL BERNSTEIN

blending that's occurring throughout the industry. Big Pharma's increasing propensity to be selling injectables rather than orals, its bread and butter, also shows that these traditional distinctions are losing their relevance.

As Big Pharma has searched for acquisitions to make up for productivity challenges and revenue lost to expiring patents, it's sought to co-opt the tools of biotech. At least in Genzyme's case, the innovative spirit has been valued just as much as the portfolio and pipeline.

Genzyme's head office in Cambridge is an open-plan, beautifully-designed space that typifies the silo-busting soul of biotech. It's a far cry from the firm's modest origins in Boston's Red Light District. It also speaks to ambitious plans. If Lemtrada clears regulatory, it would suddenly give Genzyme a bona-fide portfolio in the disease state.

"We are launching two [MS] products globally and have started from a blank sheet of paper on how we are going to do business," says Sibold. "A company like Genzyme is extremely well-positioned to compete effectively and, frankly, to lead in MS, given our heritage and the way we are approaching MS."

Analysts think Aubagio, approved by FDA in September 2012, seems destined for a minority share, but some expect Lemtrada to be a blockbuster. That's due to what neurologists call SRD—sustained reduction in disability. That is, in clinical trials, not only did Lemtrada slow progression of disability, but many patients showed improvement.

"That's transformative, that you have a patient who moves back in time from where their disease was," says Sibold.

Another differentiating feature is the way the product is administered: five daily infusions and then nothing for 12 months, followed by three more daily infusions. "We've seen durable effects up to five years after that with no additional product administered," he says.

Lemtrada's development has hardly been swift. Initiated in the early '90s, it was approved in 2001 under the brand name Campath for treating B-cell chronic lymphocytic leukemia (B-CLL). But after tepid sales, Sanofi withdrew Campath last year to prevent unauthorized use in MS, much to the chagrin of some doctor groups. (The drug will still be available for free to existing B-CLL patients through a special program.) Now, it finally looks poised to reach market.

Both of Genzyme's MS drugs cleared regulatory hurdles in Europe. In June the EU granted Aubagio new active substance (NAS) designation, a move that grants eligibility for up to eight years of data exclusivity and two years of market exclusivity, and an expert panel recommended approving Lemtrada for treating adults with relapsing remitting MS with active disease. Lemtrada's label was written so that patients in need of the treatment who have active disease are candidates, with no barrier of stepping through other treatments first. "That is a real significant step forward for high-efficacy products," says Sibold. The positive opinions on both drugs now go to the EMA for ratification. FDA action on the Lemtrada application is also slated for late 2013.

Physicians expect Lemtrada to "set the benchmark for efficacy" in MS, according to a July analyst note from Leerink Swann, but to compete primarily with Biogen Idec's Tysabri, whose US sales rose 17.3% last year to $383.1 million, in a more severe patient population. It could capture some patients who fail the older therapy due to efficacy, the analysts write.

The orals, on the other hand, have similar efficacy to the so-called platform therapies—the injections, led by Teva's Copaxone, US sales for which rose 13% to $3.6 billion, according to IMS Health, followed by Biogen's Avonex, Merck's Rebif and Bayer's Betaseron.

Aubagio may edge out Gilenya in safety, but it reduced the relapse rate by about 36% in a clinical trial, less than Gilenya's 54%, and less than the 44% and 53% seen in two Tecfidera trials.

Top 10 Biologic Companies by US Sales, 2012

Rank	Product	US sales $ (millions)	% change vs. prior year
1	Amgen	$13,170.8	2.8%
2	Roche (Genentech)	$12,645.5	7.9%
3	Sanofi	$8,223.7	5.8%
4	Johnson & Johnson	$6,399.1	10.1%
5	Novo Nordisk	$6,114.8	22.5%
6	Abbott	$5,228.0	20.1%
7	Eli Lilly	$4,407.9	1.0%
8	Merck	$3,888.3	19.0%
9	Teva	$3,714.2	13.1%
10	Bristol-Myers Squibb	$2,133.9	22.7%

Source: IMS Health, MIDAS, MAT Dec 2012, US Biologic market at trade level

Biotech's Past, Present and Future

A glimpse at companies, products, key figures and other milestones in the rise of the modern biotech industry

Sources: LifeSciencesFoundation.org, MM&M research

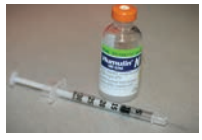
1953
Watson and Crick map the molecular structure of DNA—the double helix

1973
The era of genetic engineering: Boyer and Cohen (pictured) express recombinant genes in bacteria

1976
Genentech Inc., founded by Robert Swanson and Herbert Boyer, gives birth to the biotech industry

1980
President Carter signs the Bayh-Dole act, allowing academia to retain IP rights

1982
The first bioengineered drug, Eli Lilly's Humulin, reaches market. It was developed by Genentech



1986
Congress passes the Technology Transfer Act, which fosters partnerships between NIH and the private sector

Top 10 Biologic Drugs by US Sales, 2012

Rank	Product	Company	US sales $ (millions)	% change vs. prior year
1	Humira	Eli Lilly	$4,608.5	23.1%
2	Enbrel	Amgen	$4,336.6	15.1%
3	Remicade	J& J/Merck	$3,876.1	11.1%
4	Copaxone	Teva	$3,581.1	13.3%
5	Neulasta	Amgen	$3,459.6	4.0%
6	Rituxan	Genentech/ Biogen Idec	$3,196.7	7.5%
7	Avastin	Genentech	$2,660.8	-0.1%
8	Lantus	Sanofi	$2,326.3	12.5%
9	Lantus SoloStar	Sanofi	$2,189.3	37.3%
10	Epogen	Amgen	$2,166.8	-22.0%

Source: IMS Health, MIDAS, MAT Dec 2012, US Biologic market at trade level

"We can't compare across trials, if not direct, head-to-head," cautions Sibold, who says Aubagio's point of differentiation is that it's the only oral that has demonstrated in two studies a statistically significant effect on disability. "Neither of the other products has."

Knocking the cover off the ball

About 80% of the market is injectable, so there is plenty of opportunity in the MS space for oral therapies. Expected to gain the lion's share is Tecfidera. The pill was the third oral approved but has had an impressive launch this year, tearing up analysts' estimates. It's on track to reach at least $1 billion in sales by the end of 2014.

"I look around the industry—biotech or traditional pharma—and there were a lot of high hopes around the Pfizer arthritis drug [Xeljanz] and [the blood thinner] Eliquis from Bristol-Myers Squibb and Pfizer," says Mike Luby, founder, president and CEO at BioPharma Alliance. "So many launches that have been anticipated haven't been knocking the cover off the ball. [Tecfidera] is one where they're clearly knocking the cover off the ball."

And so far, Tecfidera is not cannibalizing sales from other MS therapies. Prescription data have shown that, since its launch earlier this year, the MS market is growing. "You could see how orals will work to really build the market," says Luby. "Over time, [Tecfidera] may chip away at others but it seems to be resulting in better care."

Considering the industry's hottest launch today can be found in biotech, the present seems well accounted for. Not that biotech hasn't seen its share of commercial success before. One of the earliest to cross the billion-dollar threshold was Epogen, Amgen's recombinant drug for treating anemia that launched in 1989. Betaseron, debuted by Chiron in 1993, was the first disease-modifying agent for treating MS.

But these drugs were first-and-foremost medical innovations. "If you were to take away those medicines, today we'd be in a much different place from a care perspective," says Sibold.

The life blood of biotech is drug development, and biotech firms will continue pushing to get drugs to market. Mid-cap companies' overall R&D expenditure rose 20% in Q3 2012 vs. Q3 2011, according to research firm GlobalData, climbing from $621.1 million to $746.8 million. Oncology was the main focus of these firms' R&D activities.

But partnering money to license those compounds has been drying up. Comparing 2012 ($2.5 billion) vs. 2010 ($5 billion) shows a 50% drop in upfront licensing payments on pipeline drugs. Such funding is impactful for small biotechs, moreso than promised milestone payments. "All this might suggest that pharmas were on a big shopping spree before the major patent expirations and mergers and has been finding a more sustainable level of deal making," says Tracy Cooley, senior director, health and emerging company policy for BIO (the Biotechnology Industry Organization).

Big issues for biotech

A decrease in financing for early-stage companies is "the single most important issue" for biotech," adds Ron Cohen, CEO of the biotech Acorda Therapeutics, who has served as president of BIO's emerging companies section. The reason for it, Cohen says: "[VC firms] draw a bright line to regulatory issues." That is, after the safety scandals involving Merck's Vioxx and GlaxoSmithKline's Avandia, the FDA went into a defensive crouch, he says.

That's why R&D productivity has suffered, he says, although now it's coming back. Last year the FDA approved 39 NMEs, and BLAs, up from 30 in 2011. And the FDA Safety and Innovation Act of 2012 compelled FDA to create its new "breakthrough therapy status," which guarantees more meeting time with senior agency officials clearing the way for an accelerated pathway to approval.

This provision originally was "against pharma's wishes," says Cohen. The impetus to advocate for breakthrough designation came from BIO, specifically from its emerging companies section, he says.

"Friends of Cancer Research championed Breakthrough Therapies," says Cooley, "but Ron is right in that BIO and our member companies were supportive of the new designation process."

On the other end of the spectrum, biotech's aging stalwarts face a big threat from biosimilars. While regulatory uncertainty still surrounds their go-to-market pathway in the US, the copycat meds are coming to a market near you. A European committee, for instance,

1989
The first biotech blockbuster: Amgen launches Epogen, a recombinant version of erythropoietin for treating anemia

1998
Genentech debuts Herceptin for HER2+ breast cancer, a big step toward personalized medicine

2003
The Human Genome Project comes to a close, after 13 years; the genomic sequence was published in 2001

2011
Genzyme is acquired by Sanofi for $20.1 billion, leaving Amgen the biggest standalone biotech

SANOFI

2013
The Supreme Court (AMP v. Myriad Genetics) rules that naturally occurring genes are not patentable

2015
When Remicade's EU patents expire in two years, it could trigger a biosimilars wave in oncology too

Biotech marketing in the age of the orals

As Big Pharma encroaches into biotech's backyard, once-staid specialty categories are seeing an advertising renaissance in terms of channel relevance and creative.

For instance, Novartis' Gilenya MS pill took a print, digital and social-channel approach tuned to the MS space, in which a much larger portion of newly diagnosed patients are between the ages of 25 and 44, and two-thirds are women.

"They're much more empowered and expect a lot more," says Dagmar Rosa-Bjorkeson, VP & head of the US general medicines MS business unit at Novartis. "So the tone of the visuals and the campaign entirely reflect that—a little bit of attitude. The sassy approach of 'Hey MS, Take This!' is, 'I'm still empowered. I'm the one that wants to still be in control of my life.'"

With the appearance of two more orals that are now available to treat the disease—Genzyme's Aubagio and Biogen Idec's Tecfidera—the MS market is changing quickly. And so is marketing in this category known for its biotech presence.

Sources say more promotion geared toward a digital-savvy demographic is in store. Genzyme has debuted new consumer work this summer for Aubagio, in channels including print and digital.

Whereas Gilenya's DTC advertising theme is spunky, and even a bit irreverent with its images of women sticking their pill-studded tongues out, Aubagio's effort takes a more literary approach. For patients and care partners, its "List" campaign focuses on everyday living.

When asked if Aubagio's consumer campaign is more toned down than Gilenya's, Bill Sibold, SVP, head of MS for Genzyme, replies, "I wouldn't necessarily say that…[We] feel like we are approaching it with the right tone."

The company says it conducted "extensive research on the needs of consumers and HCPs to best match the brand offering." Educational tools are in magazine format (pictured). Websites, both for people living with MS, their care partners and for HCPs, are fully optimized as per responsive Web design.

"The MS community is a pretty tight, small [one] so it allows us to be reasonably targeted with patient programming," according to Sibold.

He adds that the market can expect to see a big educational push centered around Lemtrada, Genzyme's MS biologic that is awaiting approval in the US and EU. "When you have a transformational treatment, it requires time to educate because it's a different way to think about managing a disease."

Despite such efforts, however, a major DTC effort is not in the cards for most biotech brands. "We can't afford it," says Ron Cohen, CEO, Acorda Therapeutics. "We have to do more with less in a little company like ours."

Cohen says that Acorda uses a fair amount of SEO and keyword tactics in its efforts to drive more patients to its websites. Ampyra, Acorda's drug for impaired walking in patients with MS, has been tried by 80,000 patients. The population of MS patients who are not wheelchair-bound is 200,000. So now Acorda is faced with the task of figuring out how the company can best reach those additional 120,000 patients.

"You're constantly working on educating and differentiating," says Cohen. People are "constantly confusing us with Gilenya or BG-12 [Tecfidera]."

recently recommended two biosimilars of Remicade, the infusion med sold by J&J and Merck. That was a major move, as the products were endorsed for multiple indications despite clinical data showing similarity to Remicade in rheumatoid arthritis only.

"This may be a sign that the same thing will happen soon for other biologics in oncology with multiple indications, like [Roche's] Rituxan and Herceptin," says Jay Carter, SVP, director of strategy services, Abelson Taylor. "Biosimilars are going to affect oncology in the US."

When they do, expect a "muted" pricing response, says Jeffrey Russell, North American managing director for Accenture's life sciences practice. Biosimilar manufacturers, he says, won't want to position their products as a "lower price play" when they've invested hundreds of millions of dollars in R&D.

"Resident manufacturers will challenge the new entrants to demonstrate safety and efficacy in real-market settings though having done so in the clinical trial environment," Russell adds. "Demonstration of value using real-world evidence will be critical."

An identity crisis?

Another big challenge with which biotech is grappling can be called an existential one: As it becomes one with pharma, is biotech in danger of losing its identity?

Already, Cohen says, the difference between biotech and Big Pharma is "more of a philosophy than a reality" (his own company's lead product Ampyra, a pill for improving walking in patients with MS, would be "right at home" in a pharma company, he says) and any kind of "membership" in biotech—if there is one—has to do with being a venture-backed start-up, rather than a multi-national corporation.

Rather than the kinds of products it's working on—less and less the scientific tools developed by molecular biologists—biotech, he says, is "a place for the swift, high-risk-taking company."

Researchers studying the issue have another name for it. They claim that what makes a biotech a biotech is its "culture." That formerly fuzzy attribute didn't necessarily lend itself to hard measurement, but a study by Temple's Fox School of Business offered empirical evidence of the link between culture from a commercial-operations standpoint and revenue performance. "If you acquire one of these companies, this study would say…the culture is what makes [it] productive," says George Chressanthis, PhD, a Fox professor of healthcare management and marketing who led the study team.

The results from Chressanthis et al. have implications for biopharma companies on the lookout for new acquisitions. Execs evaluating potential targets should check for their underlying culture of innovation in commercial operations, in order to allow a quantitative investment to realize its full return. And if they do witness a unique culture, says Chressanthis, "What you don't want to do is disturb that."

So far, pharma seems to get this. In 2011, Sanofi CEO Chris Viehbacher wondered if he could keep his people from exerting what he called a "Sanofizing" effect over Genzyme—layering on bureaucracy and stripping the biotech of its culture. Genzyme's MS franchise now stands as one testament that he is doing his best not to step on toes.

That means future graft-ons along the lines of Sanofi-Genzyme or Roche-Genentech can only succeed if acquisitions are followed by a hands-off approach by pharma and incentives based on what researchers produce, says Cohen. While biotech may be for sale, he thinks its identity—its DNA—will never become a mere commodity.

"Pharma has been trying to inject that spirit," the CEO says. "They haven't licked it yet." ■