Building A Fully Integrated Biotech Company: WHAT IT TAKES

The transition from R&D to a fully integrated stage is a make-or-break scenario for any biotech company. High-quality marketed products alone don't guarantee a successful transformation – it also requires strategic focus and an organization capable of delivering on that ambition.

BY JAN SKVARKA AND CHUCK FARKAS

- Typically, about 50% of the executive team turns over during the transition from R&D to fully integrated biotech, and about half of the companies that make this move destroy shareholder value during the two years following their first product launch.
- The biggest challenge for most biotech companies is adjusting from being judged on clinical progress to being judged on how they meet the financial expectations of investors. These new expectations have profound implications for strategic choices, program decisions, capital allocation trade-offs, talent choices, and organizational evolution.
- The companies that have successfully navigated these challenges typically mine existing assets to achieve their full potential; they focus on a few disease areas; they build out their licensing and acquisition capabilities; they develop a formal strategy and bring everyone on board; and they rebalance their organizations and retain key talent.

A typical mature biotech company evolves over four discrete stages – from the initial discovery stage through the preclinical and early clinical stage, then to the late clinical trials and commercial build-out – before it becomes a fully integrated biotech company (FIBCO). The final transition to full integration is a particularly critical test for the executive team.

Bain & Co. research, based on the FIBCOs among the top 35 biotech companies, shows that firms replace about 50% of executives during the transition period, defined as two years prior to first drug launch through two years after that launch. For CEOs, the replacement rate is 43%; for CFOs, it is 52%; for CSOs or heads of R&D, it is 41%; and for COOs, it is 75% (though only about one-third of the companies had a COO at the time of transition). While these statistics include both voluntary and involuntary executive departures, they reflect clearly the scope and magnitude of the challenges facing biotech executive teams during the transition to a FIBCO. (The data include biotechs that commercialized at least one drug and either had market caps of more than $3.0 billion as of June 30, 2013, or were acquired at a value of more than $3.0 billion. Executive promotions [e.g., from COO to CEO] were not counted toward the replacement rates for the departing positions.)

Shareholders of new FIBCOs have not fared any better. About half of the companies that have made this move destroyed shareholder value during the two years following their first commercial launch. For 21 biotechs that had launched their first drugs from January 2000 through June 2011 (excluding those that had fully partnered out the commercialization), 10 had increased and 11 had decreased shareholder value relative to the S&P 500 Index during the first two years following FDA approval of the drug. (*See Exhibit 1.*)

Despite the daunting odds, companies can and do manage the transition successfully. Moreover, making the move to a fully integrated model is often the only way to create substantial value.

Of the top 35 biotechs with market or acquisition values of more than $3.0 billion, 30 were fully integrated, and three (Pharmasset, **Pharmacyclics Inc.**, and **Theravance Inc.**) were still pipeline-stage companies. (Theravance did originate and co-develop one drug, *Vibativ* [telavancin], launched by **Astellas Pharma Inc.** in 2009, but the sales efforts were stopped due to weak sales in 2012; Theravance reintroduced the drug to the US market in August 2013.) (*See "Theravance Re-Introduces Vibativ In The U.S. Independently (For Now)" — "The Pink Sheet" DAILY, August 14, 2013.*) Only two companies (**Alkermes PLC** and **Isis Pharmaceuticals Inc.**) had approved products and fully relied in their commercialization on partners. (Alkermes did derive about 10% of its revenues from direct sales of *Vivitrol* [extended-release naltrexone], which was initially launched by Cephalon, but Alkermes later took over the marketing responsibility.) (*See Exhibit 2.*) (*See "Can Isis Remain A Platform Company?" — IN VIVO, August 2013.*)

Companies that have navigated these challenges successfully typically have five guiding principles in common: they mine existing assets to achieve their full potential; they focus on a few disease areas; they build out their licensing and acquisition capabilities; they develop a formal strategy and bring everyone on board; and they rebalance their organizations and retain key talent.

MINE EXISTING ASSETS TO ACHIEVE THEIR FULL POTENTIAL

Successful FIBCOs focus on finding the "gold" in existing assets, even though it may be tempting to move on to a new product once the first one is successful. The reason is that existing product assets are the best source of cost-effective and predictable revenue growth. The key tool is label expansion, which can come in different forms – earlier lines of therapy, new patient segments, or new disease areas.

Label expansion is particularly important in oncology, where new drugs are often approved for refractory indications first, and tumor types frequently share molecular origins and pathways. In fact, the top eight targeted cancer drugs derived almost 40% of their 2012 US revenues from disease areas that were not part of their initial labels. (*See Exhibit 3.*) If we also include line extensions for those drugs, the combined revenues from label expansions accounted for more than two-thirds of their total revenues.

In addition to incremental revenue, label expansion is critical for a number of other reasons. First, the source of revenue is cost-effective – it requires limited incremental discovery, fewer clinical trials, and commercialization with minimal additional resources if it is in the same disease area. Second, the probability of success is higher than it is for new molecular entities (NMEs), because label expansions build on established mechanisms of action and proven safety profiles. Finally, they are almost always faster to market than NMEs.

The typical time to market (IND to launch) is five to eight years for NMEs, but it can be a fraction of that time for additional indications. For example, **Roche** division **Genentech Inc.**'s

Exhibit 1

Post-Approval, Creating Or Destroying Value

Change in stock prices of biotechs two years following their first commercial product approval, January 2000 through June 2011.

Company	First Drug Launched*	Time of FDA Approval	Stock Price Change Relative to the S&P 500
Scios	Natrecor	August 2001	+219%**
Alexion	Soliris	March 2007	+210%
BioMarin	Naglazyme	May 2005	+104%
Actelion	Tracleer	November 2001	+97%
Amylin	Symlin	March 2005	+66%
Cubist	Cubicin	September 2003	+65%
Onyx	Nexavar	December 2005	+63%
Regeneron	Arcalyst	February 2008	+54%
United Therapeutics	Remodulin	May 2002	+47%
Vertex	Incivek	May 2011	+19%
Auxilium	Testim	October 2002	-8%***
Optimer	Dificid	May 2011	-18%
ImClone	Erbitux	February 2004	-19%
ZymoGenetics	Recothrom	January 2008	-31%
OSI	Tarceva	November 2004	-35%
HGS	Benlysta	March 2011	-56%**
Millennium	Velcade	May 2003	-60%
Pharmion	Vidaza	May 2004	-66%
Dyax	Kalbitor	November 2009	-66%
AMAG Pharma	Feraheme	June 2009	-76%
Dendreon	Provenge	April 2010	-82%

*Includes only drugs that were commercialized by the company in at least one region.

**Based on last available stock price prior to acquisition.

***Compared with IPO price.

SOURCES: Compustat; Bloomberg; 10-Ks; FDA; Bain analysis

Exhibit 2

The $3 Billion Biotech Club

Top biotechs, both independent and acquired, by market value (>$3.0 billion); shaded companies were acquired; italicized companies are R&D stage only.

#	Company (acquisition year, buyer)	Market Cap on 6/30/13 or Acquisition Value ($B)	Sales in 2012 or Last Year* ($M)	Number of Employees on 12/31/12 or Last Year*	Year Founded	Key Disease Areas
1	Genentech (2008, Roche)	102.5	13,418	11,186	1976	Oncology
2	Gilead	78.2	9,703	4,500	1987	Antiviral
3	Amgen	74.0	17,265	17,500	1980	Nephrology, oncology, immunology
4	Biogen Idec	51.1	5,516	5,950	1978	MS, hemophilia
5	Celgene	48.8	5,507	4,700	1986	Oncology
6	Genzyme (2010, Sanofi)	24.5	4,049	10,100	1981	Rare diseases, other
7	Regeneron	21.9	1,378	1,950	1988	Various
8	Alexion	18.0	1,134	1,373	1992	Rare diseases
9	Vertex	17.7	1,527	2,000	1989	Hepatitis C, CF
10	Shire	17.5	4,648	5,251	1986	ADHD, rare diseases, other
11	MedImmune (2007, AZ)	14.9	1,277	3,000	1988	Inflammatory, immunology, oncology
12	*Pharmasset (2011, Gilead)*	*11.0*	*1*	*82*	*1998*	*Hepatitis C*
13	Immunex (2001, Amgen)	10.8	987	1,618	1981	Immunology
14	Chiron (2005, Novartis)	10.5	1,723	5,400	1981	Rx, IVD, vaccines
15	Millennium (2008, Takeda)	8.4	556	1,100	1993	Oncology
16	BioMarin	7.7	501	1,002	1997	Rare diseases
17	Amylin (2012, BMS)	7.1	651	1,300	1987	Metabolic
18	Actelion	6.8	1,890	2,391	1997	Rare diseases
19	ImClone (2008, Eli Lilly)	6.5	591	1,128	1984	Oncology
20	Onyx	6.3	362	420	1992	Oncology
21	*Pharmacyclics*	*5.8*	*82*	*224*	*1991*	*Oncology*
22	Centocor (1999, J&J)	4.9	338	1,200	1979	Immunology, CV

Exhibit 2

The $3 Billion Biotech Club (continued)

#	Company (acquisition year, buyer)	Market Cap on 6/30/13 or Acquisition Value ($B)	Sales in 2012 or Last Year* ($M)	Number of Employees on 12/31/12 or Last Year*	Year Founded	Key Disease Areas
23	OSI (2010, Astellas)	4.1	441	512	1992	Oncology, metabolic
24	MGI Pharma (2007, Eisai)	3.9	343	540	1979	Oncology, acute care
25	*Alkermes***	*3.9*	*576*	*1,230*	*1987*	*CNS*
26	*Theravance*	*3.8*	*136*	*226*	*1996*	*Respiratory, other*
27	Seattle Genetics	3.8	211	538	1997	Oncology
28	Medivation	3.7	159	121	1995	Oncology
29	Abraxis (2010, Celgene)	3.6	359	885	1991	Oncology
30	HGS (2012, GSK)	3.6	187	1,100	1992	Various
31	United Therapeutics	3.3	916	623	1996	Rare diseases, oncology
32	Ariad	3.2	558	300	1991	Oncology
33	Pharmion (2008, Celgene)	2.9	239	417	2000	Hematologic oncology
34	Cubist	3.1	926	762	1992	Antibacterial
35	*Isis*	*3.0*	*102*	*288*	*1989*	*Multiple disease areas*

*For acquired companies, figures are for the last year prior to acquisition.

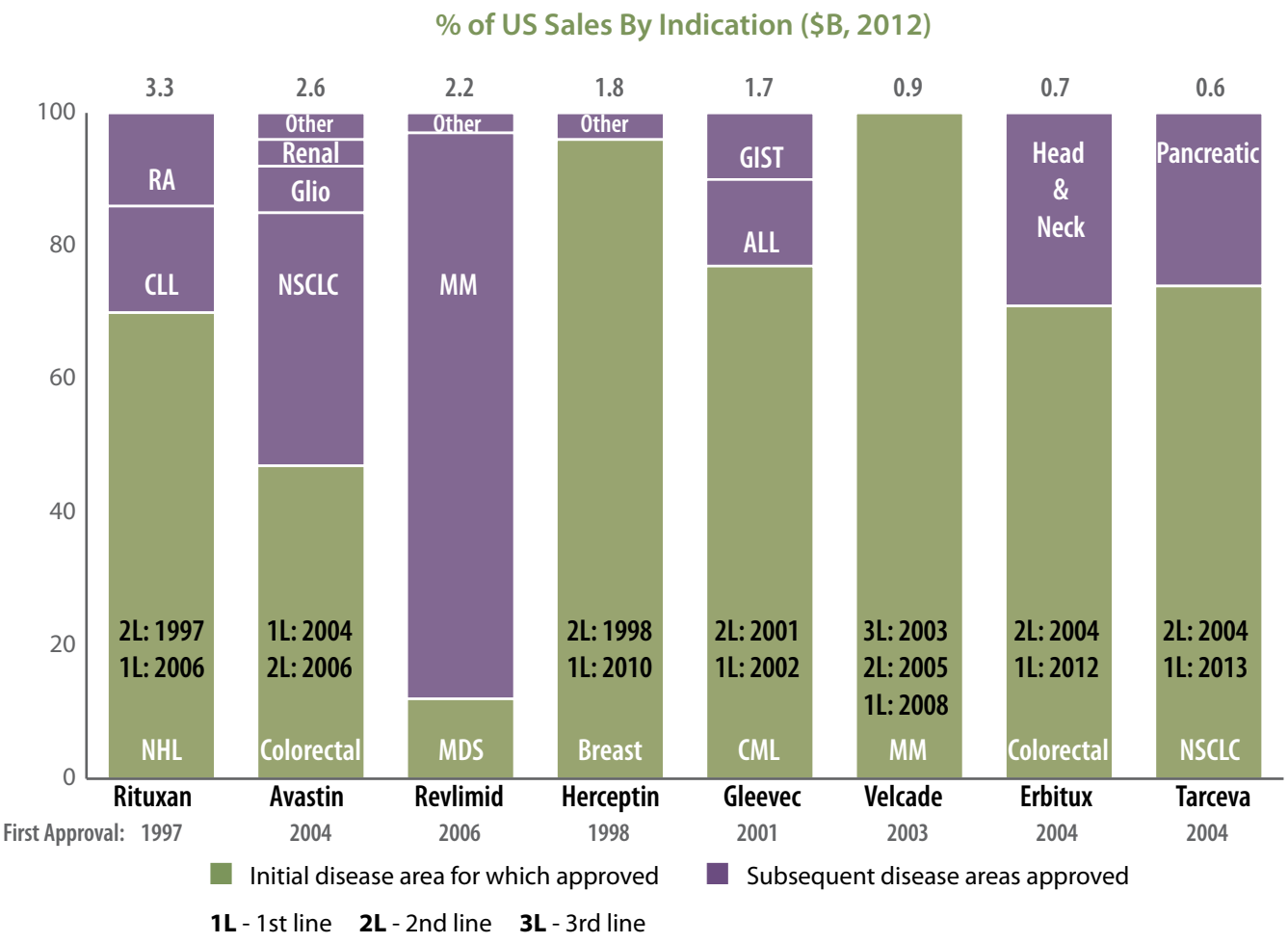
**Alkermes does have limited commercial capabilities, deriving about 10% of its revenues from product sales.

Note: Biotech company defined as company with research capabilities (i.e., does not include specialty or generic pharma companies) and established after 1976 (post Genentech).

SOURCES: Capital IQ; Dealogic; 10-Ks; Company press releases

Exhibit 3

Top Targeted Oncology Drugs By Label Evolution



SOURCES: EvaluatePharma (specific indication sales based on analyst estimates); BioMed Tracker; FDA

Avastin (bevacizumab; IND filed in 1997) was approved for first-line metastatic colorectal cancer in 2004; in the subsequent five years, the company added five more indications to that label (second line mCRC and NSCLC in 2006, HER2-breast cancer in 2008, and glioblastoma and mRCC in 2009).

FOCUS ON A FEW DISEASE AREAS

Focus is the single most important factor in creating and sustaining a true competitive advantage in business. Biotech executives, however, often argue that their industry is different, that the random nature of the R&D and business development requires them to seize random opportunities. While this randomness may indeed generate a unique opportunity from time to time, more often than not, such claims are the result of a lack of strategy, direction, or ability to create a true competitive edge.

In the majority of cases, the most powerful focus for a FIBCO is on a disease or therapeutic area – although this is not always intuitive to emerging FIBCO executives, many of whom became successful by focusing on a discovery platform and exploring multiple disease areas before selecting a lead product. However, once a biotech reaches a fully integrated stage with a comprehensive commercial infrastructure, shifting between unrelated disease areas becomes too costly.

Three of the most successful biotechs are good examples of companies that reaped the benefits of focusing on a disease or therapeutic area, albeit in different ways: Genentech, through a deep understanding of the biology of cancer and systematic label expansion of its drugs into new cancer indications, achieved success in oncology; its geographic focus on the US and related proceeds from Roche partnership provided additional leverage. **Gilead Sciences Inc.**, through fixed-dose combination therapies based on its lead HIV product, *Viread* (tenofovir), and by later creating a comprehensive, industry-leading Hepatitis C virus (HCV) pipeline via acquisitions, leads in antiviral therapy without losing its overall focus. And **Celgene Corp.**, by developing analogs of a platform drug, thalidomide, and supplementing those with strategic acquisitions, created a winning position in hematologic oncology. (*See sidebar, "Celgene: Building on Thalomid."*)

To mitigate the risks of focusing on a disease area and the potential to be disrupted by a new market entrant, successful biotechs target their disease area focus from multiple angles. For example, **Regeneron Pharmaceuticals Inc.**, which recently launched *Eylea* (aflibercept), a wet-AMD drug, is now licensing back the ophthalmology rights to two antibodies it discovered but partnered for a range of therapeutic applications with **Sanofi** in 2007. Its goal is to build a broader ophthalmology franchise. (*See "Finally A FIBCO, Regeneron Sets Its Sights On* Eylea *And Beyond"* — IN VIVO, *March 2012*.) Genentech (though now belonging to the Big Pharma ranks) uses this approach through its "multiple shots at goal" strategy in hematologic and breast cancers.

For FIBCOs, focus can also be based on other strengths, such as a target class or a platform. Such focus is most viable in rare diseases, where a company's commercial infrastructure is relatively inexpensive. For example, both Genzyme Genetic Diseases and **Shire PLC**'s Human Genetic Therapies unit built their businesses by focusing on enzyme replacement therapy platforms. And **Vertex Pharmaceuticals Inc.**, with a strong culture of innovation and expertise in structural biology and several target classes, has been successfully expanding from HCV to cystic fibrosis, albeit the latter under an orphan drug designation.

BUILD OUT LICENSING AND ACQUISITIONS CAPABILITIES

Once a biotech moves beyond the R&D stage and becomes a revenue-generating company, investors start expecting predictable revenue and profit growth. While the first commercial year is focused primarily on executing the launch, investor attention gradually shifts to long-term revenue and profit prospects.

For mature biotechs, the internal R&D engine is no longer capable of producing the top- and bottom-line growth at the level of regularity and predictability investors expect. Although internal discovery is the most powerful value creator, it is too volatile to achieve predictable growth over an extended period of time. That is why FIBCOs have to use licensing and acquisitions (L&A) strategically to supplement their internal growth engines.

Most top FIBCOs have used L&A to boost their revenue growth. (*See Exhibit 4*.) Even Genentech, with arguably the most productive discovery engine in the industry, derived about 40% of its product revenue from drugs sourced from third parties, primarily through licensing. Only Vertex and Regeneron derived all of their revenues from internally sourced products; however, they are still in fairly early stages of their life cycles. For the top 10 biotechs as a group, the combined share of externally sourced product revenue was approximately 50% in 2012 (or the last year for which data were available if the company was acquired).

Ideally, using the L&A process to complement the portfolio with outside products would start before a "FIBCO-to-be" launches its first commercial product, as soon as there is reasonable probability of the anchor product's approval. However, given the realities of financial and managerial bandwidth constraints, most biotechs start this process once the first drug has been successfully launched. For example, Regeneron licensed back those ophthalmology rights from Sanofi earlier this year, about 18 months after its Eylea launch (and six years after the initial deal). Similarly, Celgene acquired Pharmion to further build its MDS presence in 2008, about three years after its Revlimid launch.

DEVELOP A FORMAL STRATEGY AND BRING EVERYONE ON BOARD

Strategy is the science and art of allocating scarce resources. During the early stages of a biotech's life, resource allocation tends to be focused on which programs to prioritize. Program prioritization is typically a return-on-investment (ROI) decision, made within the constraints of available funding.

Nearing the commercial stage, however, the decision making for the executive team becomes more complex, with different functional areas making demands for resources. For example: should we go direct in Europe or start a new clinical program? Should we build our own manufacturing capabilities or make a major product acquisition? Should we boost internal discovery or allocate more funds to in-licensing? Should we establish a direct presence in Japan or strengthen the supply chain?

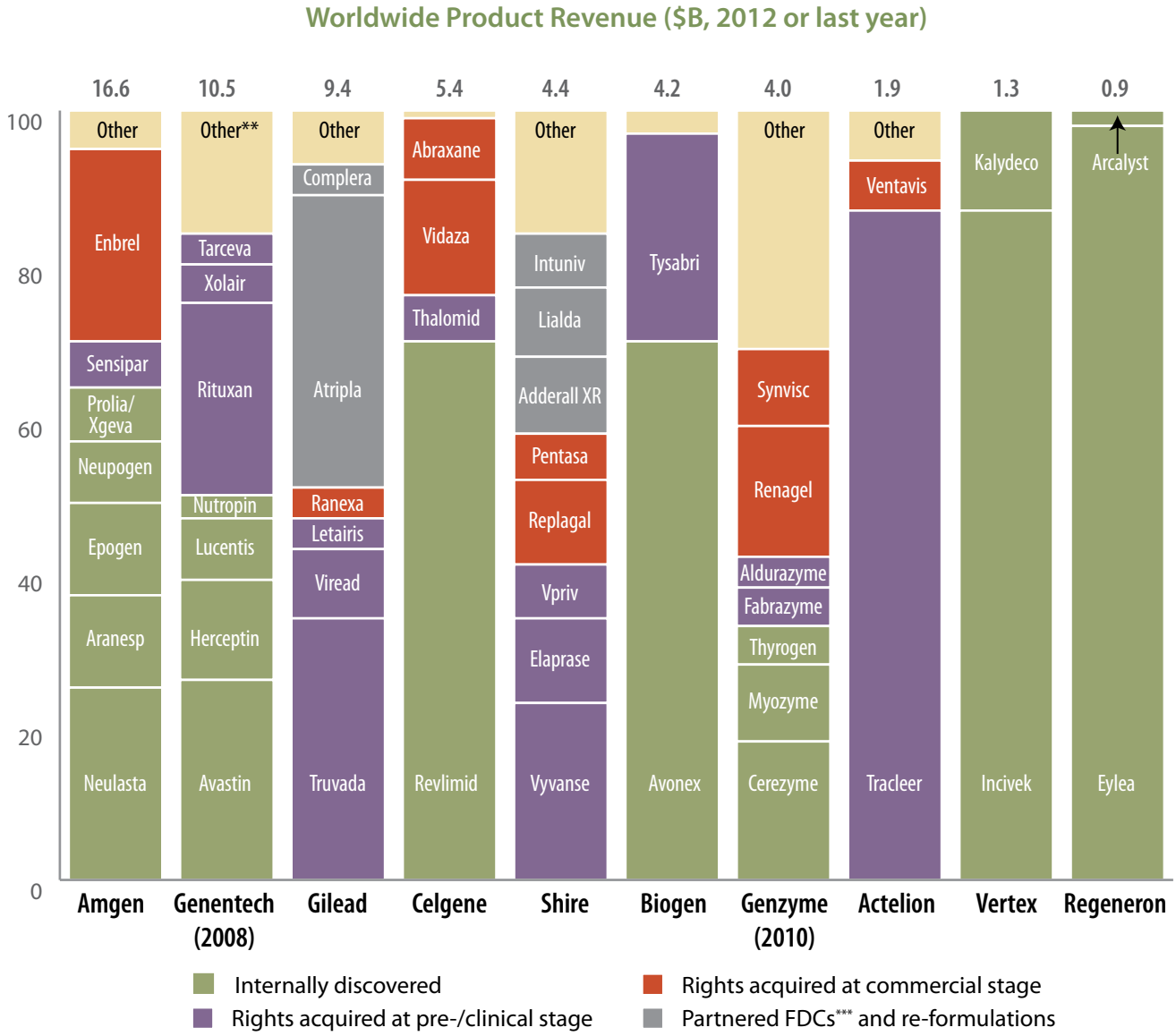
An ROI analysis will not answer these questions adequately. Making such complex trade-offs requires a formal strategy and a process to align the entire management team around the issue. Without that alignment, there is a risk that the team will get stuck at

CELGENE: BUILDING ON THALOMID

Celgene Corp. has been systematically attaining leadership in hematologic oncology on the heels of a single drug, Thalomid (thalidomide), previously used for leprosy (initially launched as an antinausea and sedative drug in the 1950s; it was later withdrawn from the market due to serious side effects and then reintroduced for leprosy in the 1990s). Based on the anti-angiogenic insights developed at Boston Children's Hospital, Celgene recognized the molecule's potential in hematology. Subsequent development work resulted in approval of Thalomid for first-line multiple myeloma (MM) in 2006, approval for Revlimid (a modified thalidomide molecule) for myelodysplastic syndrome (MDS) in 2005 and second-line MM in 2006, and approval of Pomalyst (another thalidomide analog) for third-line MM in 2013. To further strengthen its leadership position, the company made strategic acquisitions. In late 2007, it acquired Pharmion for $2.9 billion, and with it the drug Vidaza (azacitidine), indicated for several MDS subtypes. At the end of 2009, the company spent $640 million buying Gloucester Pharmaceuticals, which brought in Istodax (romidespin), a lymphoma treatment. In addition, the company is testing Revlimid in leukemia and lymphoma. Today, Celgene is the fourth-largest biotech – fifth-largest, if we also count Roche's Genentech Inc. – based on its market cap of $49 billion (as of June 30) and sales of $5.5 billion in 2012.

Exhibit 4

Sources Of Product Revenue For The Top 10* Biotechs



*As measured by revenue; **Includes $1,028M "net product sales to collaborators"; ***Fixed Dose Combinations

SOURCES: EvaluatePharma; 10-Ks; US Patent and Trademark Office; *The Amgen Story* (David Ewing Duncan, Tehabi Books, 2005); Bain analysis

each major decision point or each decision will take team members in different directions. That kind of tension and lack of consensus can contribute to executive turnover and sabotage the next stage of the company's development.

Because a strategy is only as good as the management team alignment around it, strategy must be co-created and co-owned by the entire team. And that requires a substantial time commitment. One of our clients, a major biotech company, recently undertook a broad strategic review of its business, which took 10 executive team-days to complete. Building a cohesive strategy also requires a facilitated and structured process, supported by a rigorous fact base. Without good data, creating strategy can be an exercise based on personal – and often biased – opinions.

We find that a good strategy includes the following components: vision, where to play, how to win, required capabilities, and organizational enablers. To illustrate, consider Genentech's strategy from the late 1990s, just as the company was commercially entering the oncology market with *Rituxan* (rituximab) and *Herceptin* (trastuzumab). (*See sidebar, "Genentech's Late '90s Strategy."*)

When is the right time to put a formal strategic planning process in place? There is no "right" timetable. Although most biotech companies formalize the role of strategy about a year prior to going commercial, some (e.g., Vertex) do so as early as two years before and others (e.g., Celgene) do so as late as the time of their first product launch.

GENENTECH'S LATE '90S STRATEGY

VISION:
"In Business for Life," with a strong patient and research driven mission and a "5x5 plan" – goals the company planned to achieve by 2005:
25% average annual non-GAAP earnings per share growth;
Five new products or indications approved;
Five significant products in late-stage clinical trials;
$500 million in new revenue from strategic alliances or acquisitions;
25% non-GAAP net income as a percentage of operating revenues.

WHERE TO PLAY:
Mostly humanized monoclonal antibodies; primary focus on oncology and cardiovascular; commercial presence in the US and partners outside the US, with opt-in rights exercised by Roche for the majority of Genentech Inc. products.

HOW TO WIN:
Research-driven innovation; big bets on technology; first-in-class products; speed to market via narrow label first, then systematic label expansion; medical focus; aggressive pricing; emphasis on services ("selling is secondary").

CAPABILITIES:
Deep disease biology and pathway knowledge; world-class biologic manufacturing; medical strength.

ORGANIZATIONAL ENABLERS:
Culture of innovation; close ties to academia; technological collaborations; decision making pushed down; best talent in the world.

REBALANCE THE ORGANIZATION AND RETAIN KEY TALENT

As the scope and pace of decision making change, the executive team of an emerging FIBCO must wrestle with new structural and cultural issues. What type of organizational structure best suits the new company? Who should make what decisions? How should we recruit new talent while retaining the talent we already have? The size of the management team also changes dramatically from what it was in the early days, when everyone could sit around a small conference table, to a much larger team, which may include representatives from overseas markets and the head of sales and marketing, in addition to the CEO, CFO, the head of R&D, and the chief marketing officer.

Companies will make mistakes at this stage. It's inevitable. But the experiences of successful firms offer some important tips about how to build a high-performance organization that can sustain itself through even the most challenging times.

Building out the FIBCO's management team is the first and most critical step in organizational rebalancing. However, adding new players to a management team can be disruptive. This risk is further elevated when you add new functional areas and hire new executives from other industries, like Big Pharma. Based on our interviews with executives and board members of biotechs that have recently gone through the FIBCO transition, the greatest mistake a CEO can make when expanding his or her team is to overemphasize a candidate's specific experience and underestimate the importance of cultural fit.

The development of functional silos is a very real risk for any new FIBCO. Just at the moment when the organization needs maximum flexibility, the impetus to separate out activities into their component departments gains momentum and is likely exacerbated by bringing in new management team members who want control over certain parts of the business. To prevent this problem, the chief executive of one of our recent clients created as many opportunities to use cross-functional teams as possible and gave team members responsibilities for one-off projects outside their primary functions. Addressing the silo risk directly is important in the early years of a FIBCO, before the "organizational cement" is dry. Once hardened, these silos are very difficult to break apart.

The decision-making process needs to change, too. By going commercial, the everyday dialogue within the executive team takes a U-turn, shifting from clinical progress to commercial and operational discussions. This may push some team members outside their comfort zones, and as a result, key commercial decisions may be postponed or not made at all. To address this problem, executives need to push down decisions gradually, and top management needs to evolve from being order-givers to being resource managers. Biotech executives and board members cite the inability or lack of willingness to adjust decision-making styles as the key reason for the high executive churn during the FIBCO transition phase.

Shoring up the finance function will help the company survive under the quarterly microscope of investors. This requires more stringent cost controls and reliable revenue shortfall warning mechanisms. Cross-functional trade-offs necessitate more complex analytical support and comprehensive scenario planning that is more closely linked to the strategy and commercial functions. Furthermore, direct presence outside the US will increase financial complexity exponentially.

Finally, keeping your talent is imperative. A growing and increasingly complex organization will have an impact on company culture. Some employees may prefer the old, less formal environment, and by making it to the FIBCO stage, they may be wealthy enough to consider other career options. In this situation, formal employee feedback systems can help keep the pulse of employee morale and loyalty, and allow the executive team to intervene appropriately when problems arise.

Given the volatile nature of the biotech business, not every company will make a successful transition to full integration. Although scientific and clinical uncertainty is the primary factor influencing success or failure in the R&D stage, the right strategic choices and sound management practices will be the dominant success factors for a FIBCO. Short of the occasional great product that can paper over a lot of failures in execution, companies would be wise to rely on strong execution and effective management tools to ensure a successful transition to a FIBCO. IV

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