

IN VIVO

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Big Pharma's Large Molecule Future

An extraordinary series of biologics deals reflects both the surging value of large molecules and the severity of pipeline anemia. Meanwhile start ups are—delightedly—revaluing their term sheets.

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BIOPHARMA: BEYOND THE FIRST PRODUCT

There are no guarantees for sustainable growth beyond first product commercialization, but there are steps companies can take to improve their chances of becoming the successful players of tomorrow.

BY PIERRE JACQUET AND JONATHAN HODGSON

- The commercialization of a first product is a critical event that attracts investors and boosts valuations but it doesn't necessarily predict which companies will withstand the Darwinian pressures of the biopharmaceutical industry.
- To succeed, companies need to stay focused on a therapeutic area, bringing a succession of drugs into clinical trials and/or identifying additional indications for their initial compound.
- Aggressive deal-making that boosts the bottom line and extends the pipeline is essential for sustained growth.
- A slow and steady march to profitability rather than a rush to positive earnings gives a company time to fund the R&D and licensing transactions that are necessary for continued performance over the long haul.

EXECUTIVES AT FLEDGLING BIOTECH AND SPECIALTY PHARMA companies strive to develop lead products with blockbuster potential in the hopes that soaring product revenues will translate into years of sustained growth. Unfortunately, the recipe for success is rarely that simple. Companies must exquisitely manage the commercialization of that first compound. In addition, they must also develop a deep enough pipeline—either by investing in home-grown research and development or by smartly in-licensing compounds. The challenge for these nascent companies comes in managing this difficult dance, all the while moving on a path toward profitability.

Figuring out what needs to happen—and when—can be a daunting task. But by analyzing the lifecycles of 32 publicly traded biotech and specialty pharma companies, it's possible to identify 5 factors that distinguish the ultimate winners from the underperformers in the marketplace. Beyond commercializing that first product, companies must remain focused on increasing their revenue, either by finding additional lucrative indica-

tions for the original drug or by debuting a succession of new products. Executives must act opportunistically and aggressively, taking full advantage of favorable market conditions when they exist, to ink deals that will boost the bottom line and extend the pipeline. And whether companies choose to build the pipeline organically or by acquisition, it never hurts to have multiple compounds at various clinical stages in order to hedge development risk. It's even better if the products all target the same therapeutic area, say just oncology or just antivirals. Not surprisingly, that focus makes it easier and more cost-effective to identify partners, train a sales force, and design clinical trials than if the company were to develop drugs aimed at very divergent patient populations. Finally, a slow and steady approach to profitability, with a continual emphasis on bolstering the product pipeline, appears to be another trait shared by biopharma winners.

THE LIFECYCLE OF A BIOPHARMA COMPANY

Emerging biotech and specialty pharma companies typically pass through three distinct stages as they mature. The first stage, or R&D-driven stage, begins when the company assembles a portfolio of home-grown and/or externally-acquired products, and ends when it commercializes the first compound. More than 90% of biotech companies today belong in this category. Companies at this stage are focused on research, clinical, and business development and often come with a heady, tightly knit culture that fuels science. Typically the Street values publicly traded companies in this class based on expected future product revenues, with most of the focus on the firms' lead products.

The launch of a first product marks a major turning point for a biopharma outfit. The company transitions out of R&D mode and into the second stage of development, the revenue-driven stage. At this point, the company's first product generates some revenue, but not enough to make the company profitable. In addition, the firm outlays vast sums to build commercial infrastructure and manufacturing capacity, and hire an effective sales force. Typically, investors value a company at this stage based on some multiple of the revenue generated by the first product.

Companies that become profitable belong to the third and final

stage, the earnings-driven category. At this point, firms are valued on the basis of their earnings. Since investors prefer consistent, strong earnings growth, companies at this stage must focus on improving the bottom line by increasing product sales while controlling costs.

Biopharma companies in the first stage of development have greater leeway from the investment community—they are expected to burn cash, and invest in their future at the expense of earnings as they develop product pipelines. But once a company launches a product, it has less flexibility. Investors are typically so focused on the sales performance of the company's lead product that they discount the remaining development pipeline. Therefore, the foundation the company builds as it prepares for that first product commercialization is critical to its long-term performance.

THE COMMERCIALIZATION OF THE FIRST PRODUCT: A CRITICAL INFLECTION POINT

Obviously, any time a biopharma brings a product to market it's a critical event. But no occasion is fraught with more hand-wringing than the commercialization of the very first compound. That's because a product launch plays a key role in attracting investor attention and can directly impact a company's valuation. Companies that actually succeed in commercializing a product are viewed differently from their development stage brethren: they belong to a different asset class, one that has a much lower risk profile. Moreover, investors tend to trade these companies based on short-term expectations such as the weekly or monthly sales performance of a lead product. That's very different from development stage companies, where speculations around the pipeline and the technology drive trading activity. In addition, a product introduction represents a key opportunity for investor value accretion. Crunch the numbers and you'll find that the 32 companies included in this study had robust performance, achieving on average more than 250% market capitalization appreciation, and 40% stock price appreciation beyond the AMEX Biotechnology Index (BTK), a broad-based index of public biotechnology companies, in the five years following the market introductions of their first drugs.

But despite the bump in market capitalization, most companies struggled to maintain their initial success. Sustained growth remained a constant challenge, and only 19% of them consistently outperformed the biotech industry in the 5 years following the launch of their first products. (See Exhibit 1.) Based on a careful examination of the data, we divided our 32 companies into three different categories: (1) sustainable performers; (2) momentum performers; (3) underperformers.

Only six companies consistently outperformed the BTK during the five years that followed a first product launch. These sustained performers rocketed to success, outpacing, on average, the BTK by more than 700% in market cap appreciation and 250% in stock price appreciation during the critical time period. The firms now post market capitalizations in the billions.

Like the sustained performers, the momentum performers saw a bump in their market values following the introduction of a first therapeutic—at least initially. But the eight companies in this category were unable to maintain their performance for more than two to three years, and the average spike in market capitalization lasted only 20 months. Of these eight, only one had performance in excess of the market at the end of the study period, at a 60% discount to its best performance.

By far the most populated category in this study was that of the underperformers. 18 of the 32 analyzed companies belong to this group. Unfortunately, these companies reached a peak in market cap appreciation around the time they began marketing their first compounds. Five years later, the companies were consistent laggards, underperforming the BTK by 40% in stock price and 70% in market capitalization.

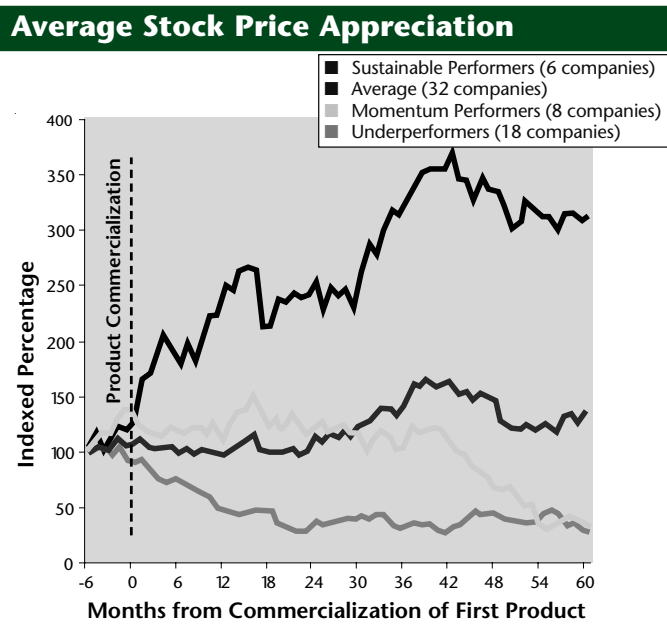
Interestingly, about 30% of the 32 companies studied—including 3 momentum players and 6 underperformers but no sustainable performers—were either acquired or merged with another entity during the five-year period that followed product commercialization. These included large deals such as Idec Pharmaceuticals Corp.'s 2003 merger with Biogen Inc. that created **Biogen Idec Inc.** in a transaction worth nearly \$7 billion in stock, as well as smaller transactions such as **Salix Pharmaceuticals Ltd.**'s \$190 million take-out of **InKine Pharmaceutical Co. Inc.** in June 2005. Such deals aren't too surprising. Just because a product reaches the market doesn't mean it's immune to competition or predation and companies facing these challenges—such as the momentum performers or underperformers studied here—are always going to find themselves on the list of potential acquisition targets.

But there is another reason for this high rate of acquisitions. Despite good lead product performance, some of these companies made the deliberate choice to be acquired by a larger organization. That's because they lacked sufficient resources to fund the R&D or business development activities that could sustain the company long term. A better option for these struggling companies: selling themselves to a bigger outfit with enough funds to maximize their product's performance.

RE-THINKING FIRST PRODUCT COMMERCIALIZATION

So, what can a company do to ensure it ends up a sustainable performer and not a momentum performer or underperformer? And what are the key drivers for value creation beyond market launch? A closer look at the histories of these 32 companies offers

Exhibit 1



Indexed to 6 Months Prior to Commercialization of First Product
SOURCE: Bloomberg, L.E.K. analysis

some illuminating lessons for building sustainable growth beyond the commercialization of a company's first therapeutic.

LESSONS 1 AND 2: REVENUE GROWTH AND AGGRESSIVE BUSINESS DEVELOPMENT

This analysis shows that the highest performing companies posted the greatest increase in revenue in that critical five-year window following a first product introduction. (See Exhibit 2.) Sustainable performers used two different strategies to maintain this tremendous growth. They were able to boost product sales of their first compound by putting it into clinical trials in multiple additional indications, as **Celgene Corp.** did for its cancer drug thalidomide (*Thalomid*), a therapeutic initially designed to treat severe erythema nodosum leprosum (ENL) and now on the market for multiple myeloma. Other companies were able to launch a

series of new products in quick succession, as **Gilead Sciences Inc.** did with injectable *cidofovir* (*Vistide*) in 1996, *oseltamivir phosphate* (*Tamiflu*) in 1999, *amphotericin B* (*AmBisome*) in 2000, and *tenofovir disoproxil fumarate* (*Viread*) in 2001. Surprisingly, a change in revenue was a more meaningful indicator of performance than was a change in earnings.

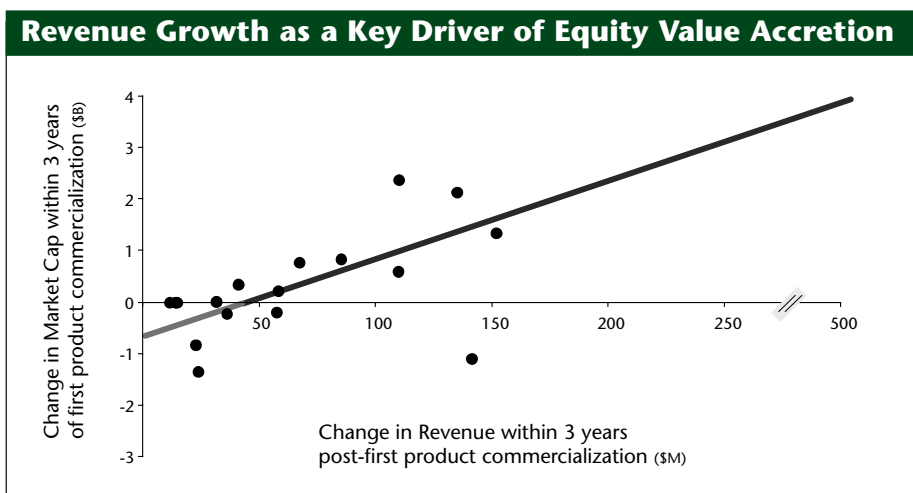
But sustainable performers did more than boost product sales. These companies made aggressive business development decisions, taking advantage of the spike in their market values to raise additional finances for future R&D, in-licensing, or commercialization expenditures. Indeed, the companies doing the most deals—either licensing transactions or money-raising efforts—belong to the sustainable performer class. (See Exhibit 3.)

Unlike the momentum players or underperformers, most of them conducted at least one follow-on public offering to raise cash after the first product commercialization. And sustainable performers didn't just tap their financial wells more often. They were also able to raise more money per event, as well as cumulatively, than peers in the underperformer or momentum performer classes.

Another key factor indicative of outperforming the BTK post-product launch: the number of transactions signed. Sustainable performers and momentum performers conducted on average 2.5 and 2.4 product transactions respectively within the first three years of marketing their first drug. Underperformers inked just 0.6 deals during this same time period. Even though sustainable performers and momentum performers did essentially the same number of deals during this critical window, their ability to do certain kinds of transactions appears to differentiate the two sets of companies. For instance, half of the sustainable performers purchased a company within 24 months of bringing their first drug to market—including **Celgene's** acquisition of **Signal Pharmaceuticals Inc.** for R&D expertise; **Gilead's** acquisition of **NeXstar Pharmaceuticals Inc.** for its antiviral franchise; and **Cephalon Inc.'s** acquisition of **Anesta Corp.** for its pipeline and delivery technology. And beyond the first 24 months, sustainable performers continued to actively broker additional acquisitions. Momentum performers and underperformers, meanwhile, rarely accomplished a company buy-out.

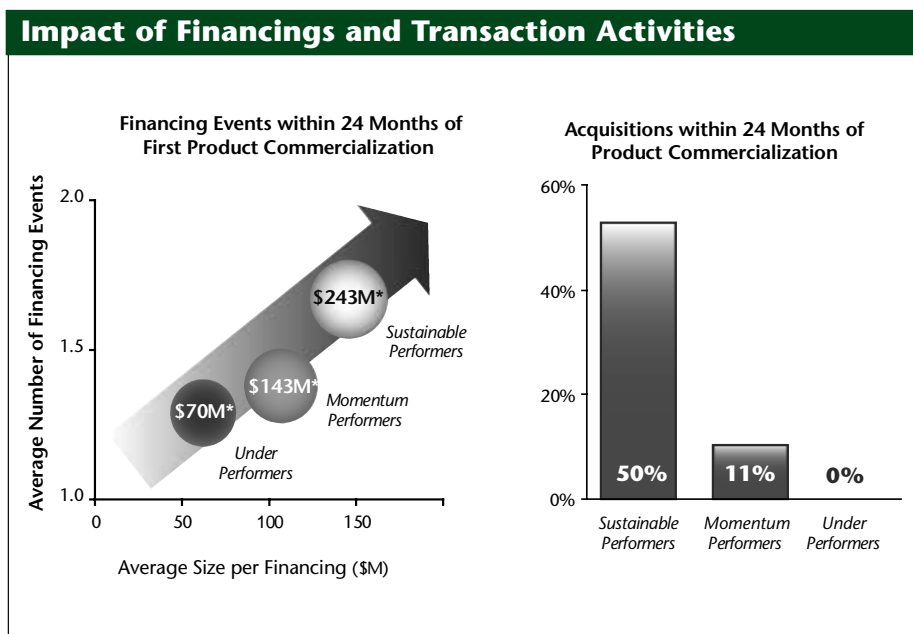
The relationship between equity appreciation following a product launch and the ability to do multiple high-value deals could be viewed as a chicken and egg scenario. Certainly companies with successful first drug launches have gained enough market buzz and increased company worth to broker business deals that wouldn't have been possible when the company was at an earlier stage. But we believe that one com-

Exhibit 2



SOURCE: Bloomberg, Compustat, Company SEC filings, L.E.K. analysis

Exhibit 3



*Size of the bubble is indicative of average cumulative amount of financing raised by company within 24 months post-PFC
SOURCE: Bloomberg, L.E.K. analysis

mon trait shared by sustainable performers is their ability to overcome the near-term inertia that stems from anticipation of a therapeutic drug launch. Indeed, these companies seemed able to carefully orchestrate a series of financings and other transactions that were critical for long term growth. For example, Cephalon licensed rights to modafinil (Provigil) from **Groupe Lafon** in 1993 (who they subsequently acquired), to tiagabine hydrochloride (Gabitril) from **Abbott Laboratories Inc.** in 1999, and to fentanyl citrate (Actiq) through the acquisition of Anesta in 2000.

LESSON 3: BUILD A PIPELINE

Unless an emerging specialty pharma or biotech company is fortunate enough to launch a blockbuster product, it must rely on additional products to sustain future revenue growth. To that end, emerging biotech and specialty pharma companies must create a critical mass of pipeline drugs to ensure their next product launch.

This analysis revealed that sustainable performers created a stronger foundation of products, as measured through their Pipeline Productivity Index (PPI), during and after the time spent commercializing their first compound. (See sidebar for a detailed explanation of how the PPI was calculated.) At the time of a new drug launch, sustainable performers had a marginally deeper pipeline than momentum and underperformers based on the PPI, achieving a PPI of 2.9, compared to 2.4 for the momentum performers, and only 2.0 for the underperformers. Three years after launching a new drug, however, there was a much greater disparity between the PPI's of the three classes of companies: sustainable performers had an average PPI of 4.8 while momentum performers had a PPI of 3.2 and underperformers had a PPI of only 2.7 (See Exhibit 4.) Interestingly, the study shows that additional drug launches—either discovered in-house or acquired through licensing—came out of stable pipelines established be-

fore these companies marketed their first compounds. One key difference, then, between sustainable performers and their less successful peers: these companies were more than one-hit wonders. They had multiple follow-on drugs and indications at various stages of development at the time they were commercializing their first compound. Celgene, for example, had seven follow-on indications in the clinic when *Thalomid* was commercialized for its lead indication in cutaneous manifestations of ENL.

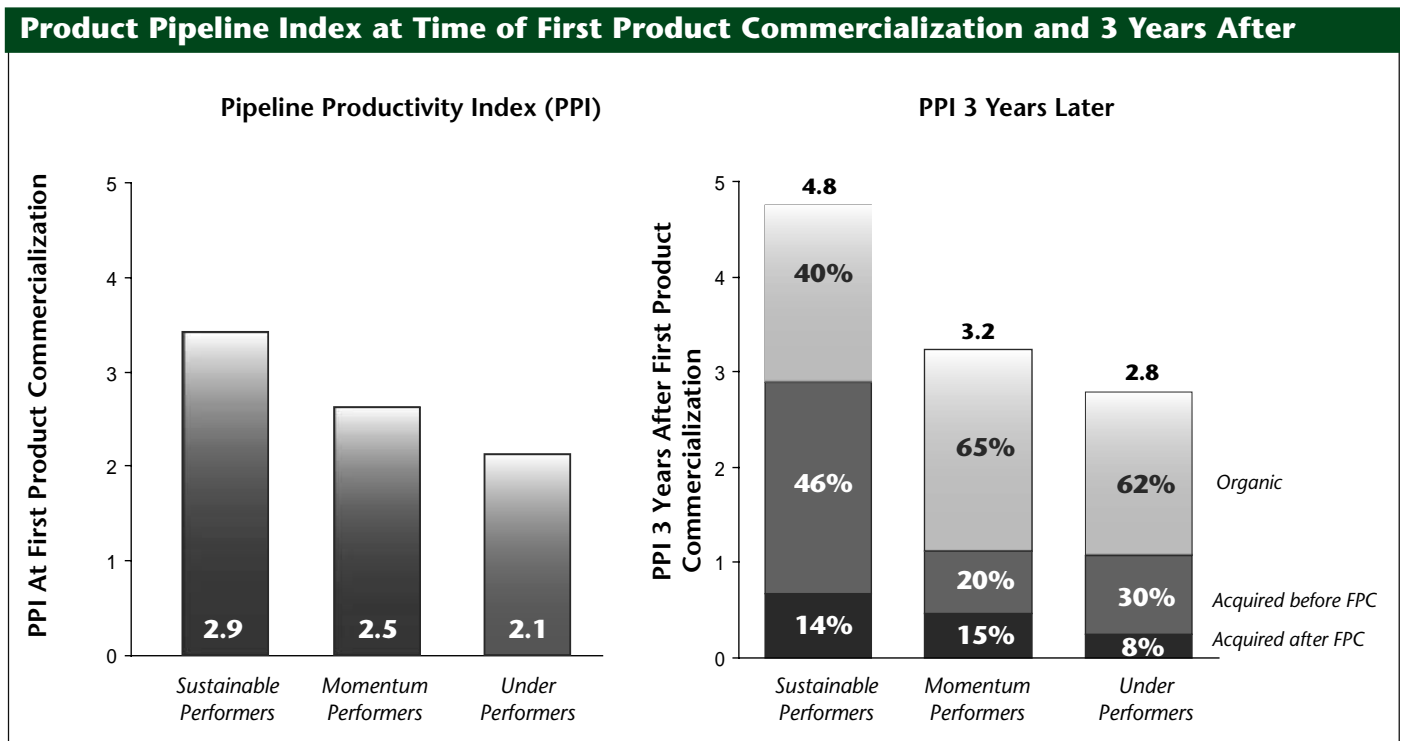
The demise of PathoGenesis Corp. (a division of **Novartis AG's Chiron Corp.**), meanwhile, illustrates the dangers of having a pipeline of one. When the company launched its first product, a broad spectrum antibiotic called tobramycin (*Tobi*) that treats lung chronic infections in cystic fibrosis patients, its pipeline was limited to a handful of early-stage compounds. In the three years that followed, it was impossible for the company to make much headway advancing the drugs, and in August 2000 they were acquired by Chiron for \$729 million.

LESSON 4: THE BENEFITS OF FOCUS

It's hard enough to develop a novel compound and get it on the market. It's infinitely more difficult to repeat this process for compounds that treat very different diseases: not only are the markets likely to be divergent, but the clinical trials required for their approval are also likely to be dissimilar. Not too surprisingly, most sustained performers adopted focused business development strategies, opting to build expertise in just one therapeutic area. **United Therapeutics Corp.**, for example, successfully managed the lifecycle of its pulmonary hypertension lead product, treprostinil sodium (*Remodulin*), through a wave of worldwide approvals, post-marketing trials, and reformulations. Gilead, meanwhile, commercialized three anti-viral products in the five years following the launch of its AIDS-support cytomegalovirus drug, *Vistide*.

Focusing on a targeted market allows a company to create

Exhibit 4



SOURCE: Bloomberg, Company web sites, L.E.K. analysis

THE PIPELINE PRODUCTIVITY INDEX

The Pipeline Productivity Index (PPI) shown in Exhibit 4 is the sum of the number of products multiplied by the probability that those products will reach the market. To calculate the probability of launch, we took into account stage of development, type of molecule (for instance, biologic or small molecule), and the therapeutic category. A product in clinical trials for multiple indications has a higher PPI than a product targeting just one disease, because each indication is included in the calculation.

CRUNCHING THE NUMBERS

In order to identify the critical actions that appear to be tied to success in the biopharma industry, we analyzed the landscape from 1996 to 2004 to identify all the publicly traded companies that launched their first products in the US. These companies have current market capitalizations ranging from under \$50 million to more than \$10 billion. To be included in this analysis, companies had to meet three requirements: (1) the firm had to be listed on some US Exchange at the time it launched its first product; (2) that product had to be the company's first significant commercialization effort; and (3) the product had to be a novel therapeutic agent—not a generic, over-the-counter, or diagnostic product. 38 companies met these initial criteria, but subsequent analysis showed that 6 were acquired too soon to their first product commercialization for the company performance to be apparent. These six companies were excluded from further studies, leaving 32 companies in the analysis.

We next compared the performance of these companies across both stock price and market capitalization with the performance of the BTK. We used market capitalization, in addition to stock price, to be sure we captured the impact of company acquisitions and stock issuances – events which can dramatically affect a company's profile. To isolate the performance of each company from the background performance of the market, each company's change in stock price or market capitalization was adjusted for the underlying performance of the BTK during the relevant time period on a month-by-month basis. Because the launch of a first product typically triggered a bump in a company's market capitalization, we normalized company stock price and market capitalizations to themselves at six months prior to first product launch. Since we adjusted each company's individual performance to the performance of the market, we were able to directly compare the performance of all companies between 1996 and 2004. We were also able to directly compare large and small companies, because we measured performance as a percent of stock price and market capitalization.

know-how that pays off in multiple areas. From a business development stand point, the company is better positioned to sign deals because they have an intimate understanding of the therapeutic arena and the different players, allowing them to ink highly competitive partnering agreements. Obviously, a focused sales force will also achieve greater efficiency with more products in a single or closely related therapeutic area, since reps only have to develop relationships with one group of physicians. In addition, as the company develops expertise in R&D, and becomes more adept at clinical trial design and working with the US FDA, it can harness that knowledge to speed the time it takes to shepherd subsequent products to market.

Sometimes this focus leads to out-licensing, as companies shed business units and improve their resource allocation. While a surfeit of ideas speaks to the vision of the executives leading the company, having too many technologies can be a distraction, making it difficult for start-ups to concentrate on the steps required to achieve lasting growth. Gilead, for example, took a very smart approach, when it divested certain interesting, but non-core, assets after its launch of *Vistide*. In 1998, for example, it sold its antisense platform to **Isis Pharmaceuticals Inc.** Three years later the company sold its oncology pipeline to **OSI Pharmaceuticals Inc.** and the 49% stake it owned in an oligonucleotide manufacturing joint venture named **Proligo LLC** to **Degussa AG**. Gilead did not “lose out” on these opportunities; instead, it raised more than \$200 million dollars to fund a burgeoning antiviral pipeline beyond its lead compound *Vistide*.

LESSON 5: DELAYING TIME TO PROFITABILITY

One other key factor in building a sustainable company: adopting a slow and steady march toward profitability. Though it may seem counter-intuitive, many companies push to become profitable too early in their lifecycles. If they focus heavily on generating positive earnings, they run the risk of stretching themselves too thin from a capital standpoint. As a result, they may not have the needed cash to fund the R&D or product acquisitions that are essential for future growth. Indeed, based on our analysis, 100% of the sustained performers ultimately became profitable, but it took, on average, 16 quarters to do so. In contrast, just 50% of momentum performers managed to do so, even though many tried to reach this elusive goal in just five short quarters. And just 33% of the underperformers became profitable, taking at least as long as the sustained performers to attain this goal. While it is clear that a company must eventually turn a profit if it is to generate value for shareholders, it also seems true that rushing to become an earnings-driven company is not necessarily optimal.

There seems to be a distinct trade-off between moving towards profitability, on the one hand, and re-investing in the development pipeline, on the other. The average emerging biotech company's ability to launch a second product and post positive earnings is driven by the threshold of revenues and cash flows generated by its lead product. Based on this analysis, a company's lead drug would need to generate at least \$750 million in peak revenue in order to have enough cash to launch a second product two years later, and become profitable a year after that. Delaying profitability by a year or two cuts the amount of revenue the first product would have to generate to \$500 million or \$300 million respectively. (*See Exhibit 5.*)

As has been said before, once a company moves into the earnings stage, investors evaluate it based on earnings multiples

and a company is invariably forced to maximize profitability rather than reinvest in the R&D and business development that will sustain revenue growth. In this instance, acquisition tends to be the end result. One example: the oncology start-up NeXstar Pharmaceuticals. In 1996, NeXstar launched its first product, daunorubicin citrate (*DaunoXome*), for Kaposi's sarcoma. A year later, it launched its second therapeutic, *AmBisome*, for fungal infections. Pressured to generate earnings following these two product introductions, the company spun-off some of its money losing research operations, into a new entity called Iterex. But the deal did little to buoy NeXstar's market performance, and a year later Gilead acquired it for \$550 million in an all-stock deal. NeXstar's story is all too familiar: 40% of the momentum performers studied here suffered the same fate. To become sustainable, therefore, companies must focus first on maximizing product revenue from their first compound before trying to move out of the red and into the black.

THE BENEFITS OF A HYBRID BUSINESS MODEL

To be long-lasting players in the biopharma industry, emerging biotechs should follow a set of key strategic principles as they prepare to market their first compound: they need to carry out multiple financing and business development transactions during the period of market appreciation; they need to build critical mass in their product pipelines at an early stage; and they need to carefully manage the Street's expectations about the time it will take to become profitable.

Beyond these defined strategic principles lurks a more subtle tenet: companies who want to thrive over the long run should

adopt a hybrid business model that incorporates the best strategies of both specialty pharma and biotech companies. Several of the companies we analyzed began as traditional biotech companies, with an emphasis on home-grown R&D and technology development. As the companies looked to market their first drugs, they also purchased new products and/or developed previously acquired products, emulating a tried and true model of the specialty pharma sector. Cephalon is a good example of a biotech company that morphed into a specialty pharma. After its first drug, insulin-like growth factor-1 (*Myotrophin*), for ALS, failed in the late 90s, the company redoubled its efforts to bring to market *Provigil*, a drug that combats the day-time sleepiness associated with narcolepsy, which it acquired from Groupe Lafon in 1993. And in the five years that followed the launch of *Provigil*, the company spent more than a billion dollars to acquire new products that could fuel the company's growth beyond its narcolepsy franchise.

In contrast, some specialty pharmas with limited research capabilities started investing in their own discovery and early stage development capabilities. Celgene, for example, followed the specialty model by in-licensing, developing and then commercializing *Thalomid* beyond its original label for cancer. Once thalidomide reached the market, however, the specialty pharma company invested in early stage R&D, increasing from \$35 million in 1998 to \$123 million in 2003, and acquiring Signal Pharmaceuticals, a deal that ultimately led to the bulk of the company's current early stage pipeline.

Flexibility and the ability to move to a hybrid model following the launch of a first product may be the right strategic choice for many players, especially when the company's first product may target a specific market that is at odds with the rest of the company's pipeline. Ultimately, however, there is no simple recipe for creating an outperformer. It's true that a company can do all the right things and still not succeed because of a lead product failure or manufacturing setback. Hopefully, the strategies outlined in this article will enhance the odds of success as companies face the diverse and challenging task of commercializing their first drug.



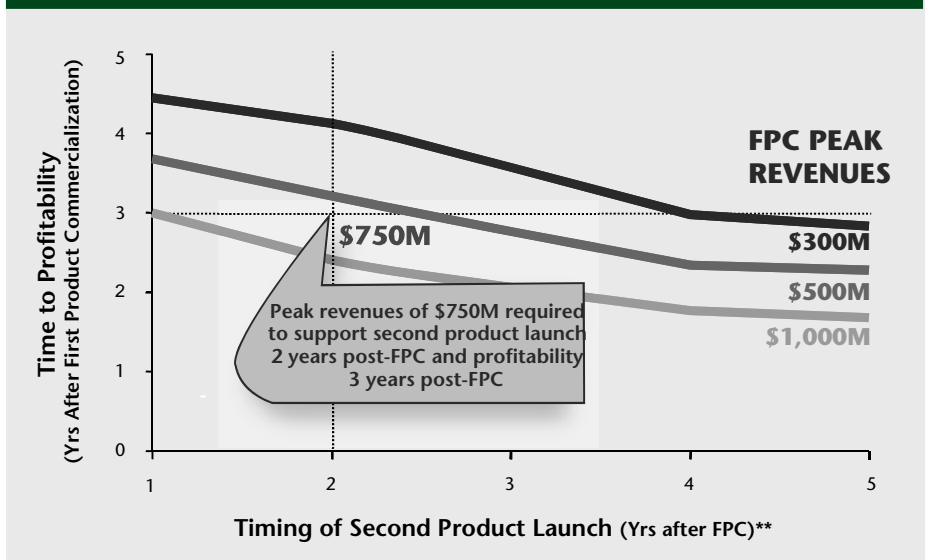
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“Though it may seem counter-intuitive, many companies push to become profitable too early in their lifecycles.”

Exhibit 5

Average Model of Productivity vs. Profitability Based on Peak Revenues



*Assumes peak revenues in 5 years; ** Timing per NDA corresponds to R&D investment
SOURCE: Parexel Pharmaceutical R&D Sourcebook, L.E.K. analysis



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