In-licensing as a business model

Dennis P. Schafer explains how in-licensing drugs can be a strategy for growing a biotechnology startup quickly and cheaply.

Scientist–entrepreneurs often ask how venture capitalists evaluate their new technologies and business plans. Optimistically, the bioentrepreneur hopes that the investor will set aside all prejudice and scrutinize the idea with fresh and eager eyes, thereby recognizing the remarkable potential of the opportunity. In reality, however, investors look at a new opportunity in much the same way as scientists regard a new discovery—with curiosity and interest but also through the filters of experience and preference. In this context, investor preferences about "business models" also apply. Here we discuss one business model that currently finds favor with investors—in-licensing.

Favorite flavors

Venture capitalists favor certain business models over others, using these as templates when evaluating new plans. An investor might reason as follows: "In my experience, model A can work if you do it right, but model B never works. And this plan looks like B—so, forget it." What the entrepreneur needs is an investor who will say, "These guys are a bit confused about their strategy, but if you change a few things this deal could look a lot like A, and A works if you do it right." The investor will then be well on his way to writing a check.

Much like scientific theories, business models go in and out of fashion. When Genentech (S. San Francisco, CA) led the industry in the early 1980s, investors were interested only in companies that could become fully integrated pharmaceutical companies (FIPCOs). When the market turned sour, FIPCOs went from Holy Grail to fool's gold. But today, FIPCOs are once again back in favor.

Indeed, business models can rise in popularity with remarkable speed—consider the recent penchant for "tool-kit" companies and any company whose technology had an "-omics" appendage. But models can also emerge more gradually, needing to prove themselves at every turn.

And the in-licensing model fits the second description. Slow to become popular, in-licensing is now fashionable with some investors, mainly because of its ability to accelerate the corporate development process. However, the model has been slow to mature, because it is difficult to find products suitable for in-licensing, and most scientists still ask, "Why bother?"

The opportunity

Although venture capitalists began making significant investments in in-licensing companies during the mid-1990s, the model has a more venerable history. On the product supply side of the in-licensing transaction, large pharmaceutical companies have for some time exchanged both launched and development-stage products with one another, swapping them in transactions that rationalize the companies' product portfolios and development pipelines. For example, a company with marketing strength in cardiovascular products might swap late-stage products with a company strong in, say, endocrinology, should a product show more promise in one clinical area than the other. Alternatively, a company that has more viable preclinical projects that it can fund, but a lack of product candidates at the phase 3 trial stage, might trade one or more of the preclinical projects as partial compensation for a candidate in phase 3.

The rising tide of mergers within the pharmaceutical industry has accelerated this trend (see Fig. 1). When two companies

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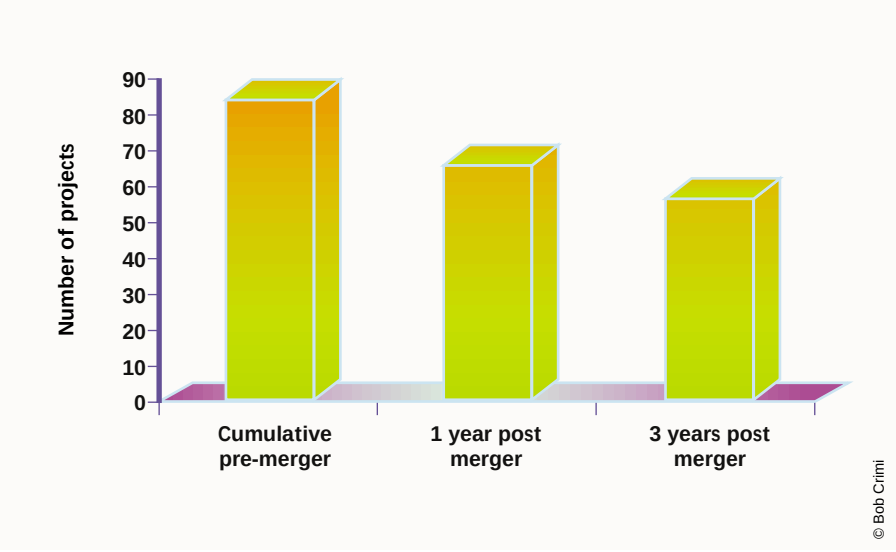

Figure 1. Number of projects in development at companies pre- and post-merger. Source: CenterWatch, *In Vivo*.

merge, inevitably good projects are cancelled and the development of certain products is halted. Indeed, in some large research-based pharmaceutical companies, out-licensing has become a formal function. Although just a few years ago most sellers would only consider licensing to other multi-national pharmaceutical companies, today they have to stoop lower in the "food chain" to find willing partners. This provides an opportunity for startups.

On the demand side of the transaction, the roots of the in-licensing business model are just as deep but perhaps less well understood. Put simply, it is far easier to build a *company* (around existing products) than it is to shepherd a scientific discovery down the long and costly path to becoming a marketable *product*. Building a company is centered on the relatively low-risk process of recruitment, which is no different for biotechnology than for any other industry. Developing new products from basic discoveries is a long, tenuous process fraught with risk. Indeed, this is attempted in few industries, and it typically fails more often than it succeeds in companies both big and small.

In fact, failure is natural and inevitable in the biotechnology industry—both technically and commercially. But companies fail less frequently than products. As the biotechnology industry has matured, a growing number of established and successful companies have emerged, which are well staffed, scientifically accomplished, well managed, and well funded—but which have failed products or technologies. Just like the emperor in his new clothes, some of these companies strut proud as peacocks down Wall Street until their stock price crashes amid snickers of recognition by investors that they have no substance and their cash reserves dry up. Some companies, short of cash, sell themselves, often just for pennies on the invested dollar. However, the wise and well funded reinvent themselves: recognizing that their original technologies failed through the attrition natural to such a risky industry, they acquire new technologies or established products and start again.

In-licensing models

The in-licensing business model originates from this process of reinvention. Typically, when companies reach this crossroad they are managed by experienced exiles of the pharmaceutical industry. These executives view this dilemma as simply another version of the pipeline problem faced by the pharmaceutical industry, and so they have addressed the problem in exactly the same way, acquiring products from the sector of the industry with which they were familiar (and sometimes even from their previous employer).

Early examples of companies that acquired launched products under these circumstances include Athena Neuroscience (S. San Francisco, CA), Gensia (Irvine, CA), and Dura Pharmaceuticals (San Diego, CA). These companies now fall into the class of so-called "specialty pharmaceuticals"—companies that acquire and market products in specific therapeutic areas such as dermatology, neurology, or respiratory medicine. Today, leaders in specialty pharmaceuticals include King Pharmaceuticals (Bristol, TN), Elan Pharmaceuticals (Dublin, Eire), and Forest Laboratories (New York), which have well-established revenues and large market capitalizations. Pharmaceutical sales and marketing are central components of this strategy—which is of little interest to scientists starting biotechnology companies—and specialty pharmaceutical companies are not discussed further in this article.

The second solution, to acquire one or more products still in preclinical or clinical development, is the origin of the in-licensing model. Companies built on this strategy may start with products fairly advanced in development, and their focus is on product development and launch. The skills involved are therefore medical and clinical, rather than relating to discovery. Typically, however, in-licensing companies do not develop sales and marketing skills, and will seek partners to commercialize their products.

The first company to make a major success of this strategy, which some might argue happened accidentally, was Agouron Pharmaceuticals (San Diego, CA). A protein crystallography company founded in 1984, Agouron formed a partnership with Eli Lilly (Indianapolis, IN) to discover antiviral drugs. In 1994, Lilly terminated the partnership, which left Agouron the owner of a Lilly compound that it subsequently advanced as its lead clinical candidate. The resulting drug, Viracept, has become a standard treatment for AIDS, and its success led to the acquisition of Agouron by Pfizer in what still stands as one of the largest mergers in the history of the biotechnology industry.

The value of in-licensing

So what are the economic benefits of in-licensing? Table 1 outlines hypothetical esti-

Table 1. Investment to product validation

	Technology startup	In-licensing startup	In-licensed product
Technology license	Stock	$1,000,000	$1,000,000
Basic research	$4,000,000	–	–
Preclinical and clinical	$1,000,000	$500,000	$500,000
Corporate build out	$10,000,000	$2,000,000	–
Total cost of validation	$15,000,000	$3,500,000	$1,500,000
Years to validation	>4 years	> 1 year	< 1 year

Source: author's estimates

mates of what it might cost to develop a product to phase 2 trials, which is not only a key stage of validation for the product but also a crucial milestone for the valuation of the company for investors.

The figures show that a company can acquire a product for a modest up-front fee, conduct preliminary tests in humans (to phase 2) for the target indication, and reach an attractive financial position rapidly and (relatively) inexpensively (column 3 of Table 1). Reaching this stage costs more, and takes longer, for a startup (column 2 of Table 1). The key difference between the two is corporate build-out—the cost of putting an organization in place. People must be recruited, which takes time, and they must be paid during the process, which takes money. Nevertheless, building organizations is something that venture capitalists are good at, making it a fairly low-risk activity. Although the cost of any component can be debated, it is clear that in-licensing is a cheaper, faster way to start a biopharmaceutical company than building one around a new technology.

More importantly, in-licensing is a faster way to reach "payoff." In venture investing, the payoff almost always occurs when the company goes public at a valuation that produces a large return on the original investment. The valuation for a *set* of public biotechnology companies plotted against their stage of product development is shown in Figure 2. The lesson is simple: the market rewards progress in clinical development, and until clinical development begins, everything is worth about the same—not very much.

The relationship between value and stage of product development has changed little over time, with slight shifts depending on market sentiment. However, the graph highlights the goals for the company founder and, critically, the founding venture capitalist: they must get to the inflection points of the curve as fast as they can and with as little investment as possible.

Today, the big inflection points are (i) initial phase 2 results, which suggest efficacy (ii) advanced phase 3 trials, which lead to a New Drug Application (NDA), and (iii) market launch. The question is which inflection point should a founder aim for? This decision is influenced by how well funded the company is. Most early stage companies and early stage investors are forced to concentrate on the first inflection point—phase 2, proof of concept. At this stage, a company can begin to offer a validated product candidate to potential partners, and can begin to talk to underwriters of the initial public offering with a straight face. At this stage, a company can also expand its private financings from a handful of early stage venture capitalists to mezzanine and crossover investors, who write bigger checks and will invest at higher valuations.

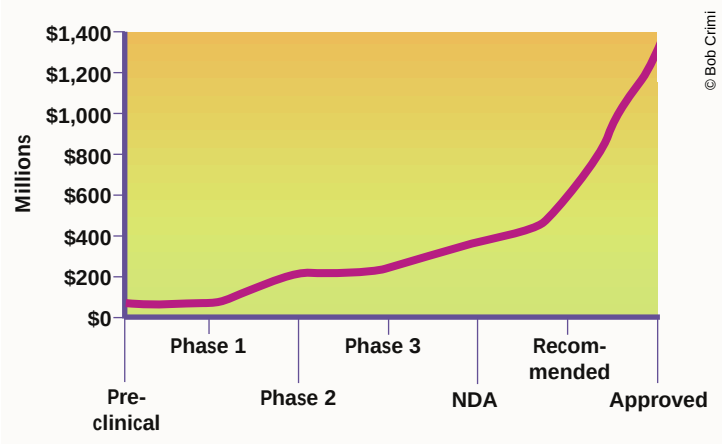

Figure 2. The valuation of a company relationship to the status of its product. Source: Burrill & Co., and Ernst & Young, 1997.

A means to an end?

Most investors would rather reach the inflection point at phase 2 after 1–2 years at a cost of $3–4 million than after more than 4 years at a cost of $15 million (Table 1). And that—in a financial nutshell—is the rationale for the in-licensing model for biopharmaceutical startups.

And that, no doubt, is where many scientists will part company with this analysis. The scientist will argue that the value of a technology startup is in its novelty and creativity and not its low cost. After all the time and investment, a scientist–entrepreneur wants a company that is more than an in-licensing endeavor. Why bother if all there is to life is developing the failed products of pharmaceutical giants?

It is a valid perspective, and a challenging question. One answer is that in-licensing is a successful means to an end. If in-licensing speeds progress, and if it is consistent with the scientific goals of the founders, it can be a tool for funding innovation, rather than an alternative to innovation.

Esperion (Ann Arbor, MI) provides an apt illustration (Table 2). Founded in 1998 with small investments by Oak Ventures and Scheer and Company, Esperion recruited a management team with proven success in developing lipid-lowering drugs and acquired a relevant late-stage preclinical drug candidate made available by the merger of Pharmacia and Upjohn. By the time Esperion went public in 2000, it had begun clinical trials on its first product, had also established its own research programs, and acquired several other cardiovascular drug candidates and technologies, some more exciting than the first candidate. By starting with a licensed product in development, Esperion made faster progress and raised more money to fund its own novel programs than likely would have been possible had the company started with promising research programs but no drug in development.

The ultimate attraction of the in-licensing model is that, done right, product acquisition brings rapid progress in product development, which allows fundraising beyond that possible for most technology startups. In turn, excess funds raised can support more aggressive development of novel technologies.

Table 2. Esperion's fundraising history

Date	Funds raised ($ million)
July 1998	0.5
August 1998	15
January/February 2000	27
August 2000 IPO	54
Total through IPO	96.5
Valuation at IPO	276

Source: SEC filings

Before you begin

In-licensing is unlikely to become a dominant model for biotechnology startups, because such ventures are always serendipitous, being dependent on the availability of product candidates. Nonetheless, the number of in-licensing businesses is increasing, and it is helpful to offer a few practical points for those considering adopting this business model.

1. You need to create an in-licensing business around people with medical and clinical development expertise, and not, as with traditional start-ups, around people focused on basic research. Expertise in pharmaceutical product development and clinical development (at least sufficient to manage these func-

tions through a contract research organization) are critical. Indeed, some in-licensing companies, notably The Medicines Company (Parsippany, NJ), have arisen to carry out clinical development faster and more cheaply than a product's originators. In-licensing companies must recruit staff from clinical development experts at large pharmaceutical companies and contract research organizations, a highly competitive sector of the employment market.

2. A second problem could be convincing a pharmaceutical giant to license its product to your little startup "gnat"; many pharmaceutical companies find it easier to swat the gnats away. You can make yourself a more attractive partner, however, by discovering value in the product that the pharmaceutical giant did not recognize. For example, in 1999, Discovery Therapeutics (now Aderis Pharmaceuticals, Hopkington, MA) acquired a discontinued phase 2 anti-asthmatic agent from Bayer (Leverkusen, Germany). Discovery had data suggesting that the product might be of value for treating kidney disease, which was further endorsed by the credibility of the company's highly regarded set of medical advisors.

3. The flow of products available for licensing is neither steady nor predictable. One way to spot potential candidates for in-licensing is to hover around newly merged companies, looking for discontinued projects or disenchanted project leaders. One company that evolved in this manner is Viropharma (Exton, PA). Pleconaril, a treatment for RNA viral diseases, was discontinued after Sanofi acquired Sterling Winthrop in the early 1990s. The scientists involved in pleconaril's development founded Viropharma, and acquired the drug in 1995, taking it into phase 3 trials. The company now has a respected antiviral discovery program. In another example, Novartis (Basel, Switzerland), which was formed by the merger of CIBA-Geigy and Sandoz in 1996, established a formal out-licensing program and a corporate venture capital fund (Novartis Venture Fund) to support former CIBA and Sandoz employees seeking to start new companies. To date, Novartis has licensed technologies to more than a dozen start-ups.

An alternative approach for identifying potential drug candidates is to forge relationships with clinicians at medical schools, who may have insights into new products that their originator lacks. Academic physicians often get access to new classes of pharmaceutical agents during very early clinical development. These experts, with their intimate knowledge of both disease and patients, may be better positioned to see how a new clinical utility will open new markets than are the pharmaceutical company's marketing department analysts.

4. To negotiate an in-license successfully, a startup must find a way to bridge the gap between the disparate values placed on the product by the licensor and licensee. Many large pharmaceutical companies set commercial hurdles before advancing a new compound into the final stages of clinical development (such as projected annual sales of $250 million or higher), which are appreciably higher than those that might be hailed a success for the start-up (as little as $50–100 million annually). Moreover, for the startup, the primary focus is not on revenue but on company value, which is driven by success in clinical development (see Fig. 2) even before the company's first product is launched. Those are the differences that make transactions work.