LAUNCH OR LICENSE: Taking Your First Drug To Europe

Directly launching a drug in Europe is the most difficult path for US-based biopharma companies, many of which decide to out-license rights for that territory. But, for the right asset, it's also the most rewarding.

BY ALAIN J. GILBERT, ROBERT J. EASTON, AND STEVEN P. BREAZZANO

- Faced with the "launch or license" decision for commercializing products in Europe, most US biotechs and small pharmaceutical companies opt for the latter, seemingly easier option.
- For an inexperienced company, running the European regulatory and reimbursement gauntlet is a formidable task, and carries significant risks and expense.
- Launching one's own drug in Europe has represented an important milestone en route to becoming a global, fully integrated pharmaceutical company, and today's improved market conditions can make this a reality sooner.
- As emerging drug companies increasingly target orphan drugs requiring smaller commercial infrastructures to market to specialist audiences, the rewards can be substantial.
- Co-promotions and profit-sharing agreements in Europe are underutilized deal structures that may add significant value.

The task of commercializing a drug alone in Europe is a formidable one for a smaller company, and licensing out European rights avoids many of the operational, regulatory, and commercial challenges. As a result, for US-based emerging biotech and pharmaceutical companies facing this decision, conventional wisdom says to simply license the European rights for a royalty stream and milestone payments. However, directly launching a drug may be the optimal option for European market entry and may add significant value to proprietary drug developers. For a forward-looking CEO, determining the right European strategy and path ahead is a defining decision, so how should one evaluate this choice?

To frame the European "launch or license" analysis and provide historical context for the discussion, we utilized the publicly available and comprehensive European Medicines Agency database. We analyzed all the drug approvals over the last 11 years (January 2003 through March 2013) and employed strict criteria to focus on the European launch versus license decision. To be included in the analysis, companies had to be US-based and either currently marketing or planning to market in the US at least one product (alone or with a partner). To minimize confounding variables, only companies where the lead or primary drug was involved in the license or launch decision were included. A total of nine companies fitting this description were identified for the launch analysis. During the same time frame, a total of 16 companies were identified that licensed their drugs in Europe for royalty and/or milestone payments while maintaining co-promotion rights or launching alone in the US. (*See Exhibit 1.*)

FINANCIAL REWARDS

With these two sets of companies in hand, we first looked at the question of overall success. Given the fact that nearly all of the launch and license companies were publicly traded leading up to and following European approval, we leveraged historical stock price information as a proxy for financial success. To account for longer-term value creation and to focus the analysis as much as possible, we examined the com-

Exhibit 1

The Dataset: 25 US Biotechs Pursuing The European Market

	COMPANY	DRUG NAME	APPROVAL YEAR
LAUNCH	Abraxis*	Abraxane	2008
	Alexion	Soliris	2007
	Ariad	Iclusig	2013
	BioMarin	Naglazyme	2006
	Celgene	Revlimid	2007
	Intermune	Esbriet	2011
	NPS	Revestive	2012
	ViroPharma*	Cinryze	2011
	Vertex	Kalydeco	2012
LICENSE	Acorda	Fampyra	2011
	Amylin*	Byetta	2006
	Auxilium	XiaPex	2011
	Avanir	Nuedexta	2013
	Epicept	Ceplene	2008
	Cubist	Cubicin	2006
	Incycte	Jakavi	2012
	Ironwood	Constella	2012
	Jazz	Xyrem	2005
	Medivation	Xtandi	2013
	Millennium*	Velcade	2004
	NeuroGesX	Qutenza	2009
	Optimer*	Dificlir	2011
	Seattle Genetics	Adcetris	2012
	Trimeris*	Fuzeon	2003
	Vertex	Incivo	2011

NPS repurchased ex-US rights to Revestive from Takeda Pharmaceuticals in March 2013. Vertex was included for both Kalydeco and Incivo given the high profile and close development time lines for both assets.

*Acquired companies (Abraxis/Celgene, Amylin/BMS, Optimer/Cubist, Millennium/Takeda, Trimeris/Synageva ViroPharma/Shire)

SOURCE: EMA Database

pany's historical stock price over a two-year time frame, beginning one year prior to EMA approval through one year post-approval. Although it often takes some time before a drug is widely available in Europe following approval, we believe this two-year window is appropriate given the forward-looking nature of the capital markets, and accurately accounts for pre- and post-approval launch plans and execution. Performance was calculated net of the S&P 500 to normalize for broader market fluctuations. For recent approvals, historical prices on November 1, 2013 were used.

While both sets of companies had large variations in stock performance, the launch companies clearly outperformed their licensing peers, and overall, this historical data clearly demonstrate that launching a drug alone may lead to significant financial reward and success. (*See Exhibit 2.*)

Overall, the majority of launch companies saw positive and meaningful share-price increases, with an average share-price increase of 48% (median 46%) over the two-year period. However, the range was considerable, from –117% to 205%, highlighting the risk and reward trade-off of the decision. In particular, **Ariad Pharmaceuticals Inc.** was a significant outperformer until recently, when safety risks caused lead drug *Iclusig* (ponatinib) to be placed on clinical hold and pulled from the market. **InterMune Inc.** has also suffered with lead drug *Esbriet* (pirfenidone) being rejected by FDA. However, on the other end, **BioMarin Pharmaceutical Inc.** is a clear success story with its recombinant enzymes, following in the footsteps of enzyme replacement therapy pioneer **Genzyme Corp.** (now part of **Sanofi**).

For those companies that out-licensed European rights to a partner, the results reveal an overall performance in line with the broader S&P 500, with an average performance of 2% (median –15%). Similar to that for the launch companies, the range was considerable, with performances ranging from –78% to 193%. Sorting stock market performances of the launch and license companies by rank order reveals clear differences between the two strategies. The launch company curve is both higher and steeper than the licensed company curve, reflecting a greater and more consistent excess value creation. (*See Exhibit 3.*)

Given the large disparity between the two sets of companies, we sought to determine if the discrepancy may be explained

by asset quality: is it simply that those biotechs with a better or more valuable asset choose the launch option? Although it's an inherently complex issue, we compared company-reported global sales data in the fourth year since European approval and these data appear to refute that hypothesis. For launch companies, the average or anticipated worldwide sales in the fourth year post-launch were approximately $535 million (median $573 million). (We used consensus analyst projections from BioMedTracker for newer drugs just entering the market and we excluded the outliers: **Celgene Corp.**'s phenomenally successful drug *Revlimid* (lenalidomide) as well as Ariad's Iclusig.) The comparable sales data for license companies reveal an average fourth-year global sales of approximately $480 million, (median $470 million), comparable to that for the launch companies, especially given that Epicept's (now **Immune Pharmaceuticals Inc.**) *Ceplene* (histamine, sold by **Meda AB**) and **NeurogesX Inc.**'s *Qutenza* (capsaicin, sold by **Astellas Pharma Inc.**) each sell under $5 million annually. Thus, it is unlikely that asset quality alone accounts for the large variation.

In addition to a positive reception in the capital markets, the dataset also reveals additional insights with profound implications for the launch or license decision. Although many hold true broadly for the launch or license decision in all geographies, the magnitude of differences in this dataset focused on the European decision is revealing. The data demonstrate that the capital markets reward successful launch companies with high valuations reflective of new-found global capabilities. These fully integrated, global companies also possess significant optionality to either launch or in-license additional assets. The data also reveal that launch companies target disease areas served by specialists and orphan indications, a fact that is unsurprising given the limited infrastructure required.

BILLION DOLLAR PHARMACEUTICAL COMPANIES

A brief glance at the list of companies in the launch chart reveals many familiar names, including BioMarin, Celgene, **Alexion Pharmaceuticals Inc.**, and **Vertex Pharmaceuticals Inc.** Since launching, the vast majority of these companies have seen large increases in share price (and market capitalization) reflecting their global reach. For many of the

Exhibit 2

Measuring (Financial) Success: Two-Year Stock Price Performance*

LAUNCH COMPANIES		
COMPANY	DRUG	TWO-YEAR STOCK PRICE PERFORMANCE
BioMarin	Naglazyme	205%
Abraxis	Abraxane	112%
Alexion	Soliris	100%
Viropharma	Cinryze	56%
Celgene	Revlimid	36%
Vertex	Kalydeco	21%
Intermune	Esbriet	–29%
Ariad	Iclusig	–117%
LICENSE COMPANIES		
COMPANY	DRUG	TWO-YEAR STOCK PRICE PERFORMANCE
NeuroGesX	Qutenza	193%
Incyte	Jakavi	89%
Seattle Genetics	Adcetris	49%
Cubist	Cubicin	41%
Vertex	Incivo	26%
Medivation	Xtandi	17%
Optimer	Dificlir	–13%
Amylin	Byetta	–15%
Avanir	Nuedexta	–17%
Epicept	Ceplene	–27%
Millennium	Velcade	–50%
Acorda	Fampyra	–51%
Auxilium	XiaPex	–62%
Ironwood	Constella	–75%
Trimeris	Fuzeon	–78%

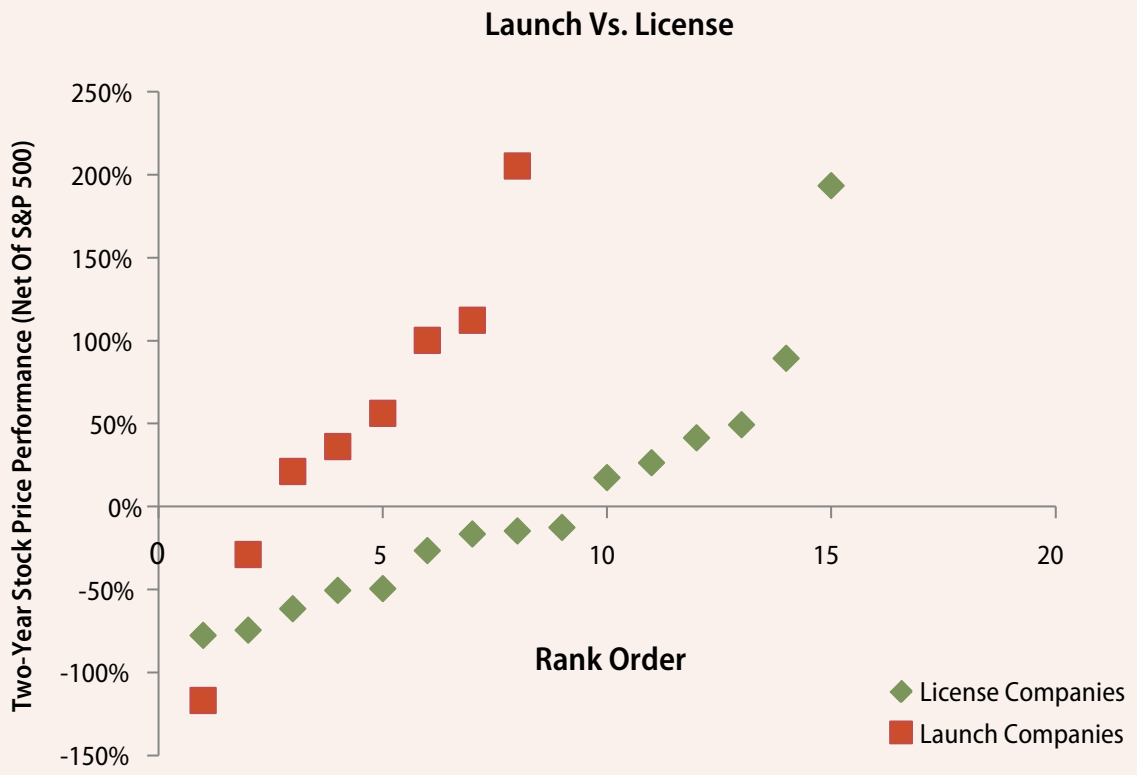
Jazz Pharmaceuticals was not included due do its private company status until 2007, and NPS Pharmaceuticals was excluded from the analysis due to the license restructuring deal in 2013 following approval.

*Measured from one year prior to EMA approval through one year post-approval. Net of the S&P 500. For drugs that launched in the past year, stock prices for November 1, 2013 were used.

SOURCE: Yahoo! Finance

Exhibit 3

Buying The Launch: Building Value By Going It Alone In Europe



SOURCE: Yahoo! Finance

firms, launching their own drugs in Europe helped to build out infrastructure and provide them the hallmark of a fully integrated, global pharmaceutical firm. Given Europe's position behind the US in terms of branded pharmaceutical spend, launching in Europe is the logical next step after the US in becoming a global pharmaceutical company.

This important milestone creates additional value beyond the asset in question, and affords opportunities for the emerging company to pursue multiple strategies. Just as this argument applies to commercializing in the US, it holds true in the global and European markets as well. For example, the sales force and related infrastructure may be used for additional pipeline drugs in Europe, a long-term strategy successfully implemented by **Biogen Idec Inc.** (multiple sclerosis focused), BioMarin (orphan disease focused), and Celgene (oncology focused).

ORPHAN DISEASES

Building a sales force and a "bricks and mortar" operation across multiple countries requires significant investment. It means building out new capabilities, including local distribution and manufacturing, in addition to sales and marketing. One way to mitigate that investment is to build a modest sales force targeting a small number of high-prescribing physicians. At the extreme end of the spectrum, a company might market a drug for an orphan disease in which only a few specialists treat patients.

Not surprisingly, of the nine launch companies identified in the EMA drug approval search, eight (89%) have therapies that have received orphan drug designation. Absent are drugs targeting large patient populations treated by primary-care physicians. In contrast, many of the companies that chose to license their drugs have assets that target indications with a larger number of prescribing physicians. Of the companies on that list, only three (18%) have therapies designated as orphan drugs by regulatory agencies.

> "Virtually all the companies that made it big historically, made it on their own. You think of Genzyme, you think of BioMarin, you think of ViroPharma: they were the masters of their own destiny and it worked very well for them."
>
> – Francois Nader, CEO, NPS Pharmaceutical

"Virtually all the companies that made it big historically, made it on their own," says Francois Nader, CEO of **NPS Pharmaceuticals Inc.** "You think of Genzyme, you think of Bio-

Marin, you think of ViroPharma: they were the masters of their own destiny and it worked very well for them."

EUROPEAN ENTRY STRATEGY

What does all this mean for management teams facing the launch or license decision? We believe that under the right circumstances, a solo launch in Europe may drive significant value for an emerging biotech or pharmaceutical company. Although the overall European entry decision and implementation steps are fairly straightforward and familiar to most executives, we recommend looking at the big picture, and placing regulatory or pricing and reimbursement risks in context.

We firmly believe that despite budgetary pressures, certain European markets remain healthy. According to the recent *Finding Value in Europe* report by LEK Consulting, the EU5 countries (United Kingdom, Germany, France, Italy, and Spain) combined will continue to represent slightly less than 20% of the branded global market spend in 2016, behind only North America (~44%). More importantly, EU5 health care spending per-capita is still high and supportive of novel therapies with demonstrated safety and efficacy. For novel drug developers, this is critical for premium-priced therapies potentially benefiting niche patient populations.

Although a recent article published in the New England Journal of Medicine found that on average the FDA approved new drugs faster than the EMA (approximately two to three months faster), minimal attention was paid to an important point: in the US, significantly fewer drugs were approved in the first review cycle. In the dataset analyzed (2001–2010), the FDA approved 62% of novel therapeutic agent applications in the first cycle versus the EMA's 96%. This demonstrates the EMA's willingness to work with drug developers through the process to ensure that safe and effective new medicines can reach the market without lengthy delays.

Overall, examining FDA approval times between our launch or license companies does not reveal any meaningful differences. On average, for both datasets, the EMA approval lags FDA approval for the majority of companies by approximately six to 12 months, suggesting that launching a drug alone is not prohibitively difficult.

For emerging biopharma companies with an eye on European marketing, there are a number of concrete actions that can be taken to ensure a reimbursed European launch. It has long been the case in Europe that regulatory approval does not guarantee reimbursement and outcomes data compared with standard of care are becoming increasingly important. This is increasingly true in the US as well. In fact, companies now looking to enter the European market may readily leverage these capabilities being developed for a US launch, given that these similar outcomes data are becoming increasingly important. The increased investment needed for acquiring European-specific capabilities is likely to be incremental, but understanding the differences and requirements between the individual European countries and the US early in the drug development process is essential.

> "Although Europe is an attractive market, the decision to partner our first drug in Europe was purely financial, but now several years later, with a strong balance sheet and an enhanced team, we are now ready to go on our own."
> – Michael Bonney, CEO, Cubist

ACCESS TO CAPITAL

Traditionally, many US-based biotechs turned to licensing agreements for European or rest-of-world rights as a source of capital to fund US operations or pipeline development. The market for biotech IPOs and secondary stock offerings has been quite subdued over the past decade, further supporting the decision to use European rights as a source of capital. In the past two years (November 1, 2011 to November 1, 2013), however, biotech valuations, as measured by the Nasdaq Biotech Index, have soared an impressive 116%, fueled by widespread and increasing optimism for the sector. This has far surpassed the 45% performance of the S&P 500 over the same time frame. Furthermore, in the first nine months of 2013, more than 30 biotech companies have gone public, raising over $2.5 billion, with several companies remaining in the registration queue. (*See "On The Road And Through The Window: Inside Three Biotech IPOs"* — START-UP, *November 2013*.) Encouragingly, nearly all these companies are trading above their IPO prices, some substantially so, though most have fallen significantly from their stock market peaks. Even so, companies with both early- and late-stage development assets are able to raise significant amounts of capital at reasonable valuations. This gives more emerging biotechs than ever the option of raising capital to further their development pipelines as well as build out commercial infrastructures at home and abroad.

Financial limitations will always impact the launch or license decision, even for otherwise strong companies. "Although Europe is an attractive market, the decision to partner our first drug in Europe was purely financial, but now several years later, with a strong balance sheet and an enhanced team, we are now ready to go on our own," says Michael Bonney, CEO of **Cubist Pharmaceuticals Inc.**

INNOVATIVE IMPLEMENTATION

Once the launch decision has been finalized, further refining the sales force requirements and determining precise personnel needs are essential to ensure a smooth rollout. But above all, the launch requires a management team with the knowledge, experience, and ability to execute. Fortunately for emerging biotechs, there are now numerous executives with the knowledge and skillset required to launch alone in Europe, many having had prior roles in Big Pharma or former emerging biotechs such as Biogen or Genzyme.

We believe there are cost-effective and efficient ways to access the required infrastructure to support the launch, including innovative virtual strategies designed to solve these operational issues while minimizing costs and commitment obligations. Recently, **Spectrum Pharmaceuticals Inc.** re-launched radiological drug *Zevalin* (yttrium-90 labeled ibritumomab tiuxetan) in the EU after acquiring its rights from **Bayer AG**. By utilizing a bespoke contract sales force trained for the specific task of marketing a radiological drug,

the company increased the speed of execution while it minimized risk, since the sales team was contracted and could be readily adjusted. Furthermore, by contracting with a third party to handle regulatory issues, Spectrum was able to avoid building a bricks and mortar European headquarters altogether.

EARLY ACCESS PROGRAMS

Prior to marketing authorization in Europe, initiating an early access program (EAP) is one strategic tool that can increase awareness and, in certain circumstances, generate revenue ahead of the official launch. These country-specific regulatory tools grant market access ahead of official launch, providing they fulfill certain criteria. A major benefit of an EAP is the ability to build relationships with customers and understand how the drug is being used in the real world prior to the full-scale launch.

Such programs are not reserved for rare diseases only, but can be initiated for any disease considered life-threatening that cannot be treated satisfactorily by currently authorized medicinal products. Previously, EAPs have been used in HIV/AIDS, neurodegenerative disorders, auto-immune diseases, and cancer. Alexion, which sells one of the most expensive drugs in the world (*Soliris* [eculizumab]), successfully utilized an EAP to drive premium pricing. Its long-term EAP provided revenue and additional data ahead of the official launch, which occurred only when it was clear that premium reimbursement would follow.

Although there are considerable challenges to overcome (significant amounts of paperwork, distribution channels, and safety concerns), there are operational strategies for overcoming these barriers, including the use of third party vendors with experience and expertise in implementing EAPs.

INNOVATIVE STRATEGIES

Beyond direct launches and licensing agreements, there are other European entry strategies that merit consideration. Although seldom used internationally, co-promotion or profit-sharing agreements are widely seen in the US between emerging biotechs and pharmaceutical firms. These partnerships provide many benefits of a licensing deal, including risk mitigation and access to Big Pharma regulatory and commercial expertise, while retaining significant financial upside.

Regeneron Pharmaceuticals Inc. has successfully implemented this strategy to create value. The big biotech struck a worldwide co-promotion deal with Sanofi (building on a previous deal with forerunner Aventis), and retains approximately half the profits from any drugs that make it to market. In addition, Sanofi provides significant funding for clinical development, and only upon commercial success does Regeneron reimburse these expenses, minimizing Regeneron's risk.

This innovative deal structure has certainly contributed to the company's $26 billion market capitalization. Another example is Human Genome Sciences (purchased by **GlaxoSmithKline PLC**). Worldwide co-promotion rights for key drug *Benlysta* (belimumab) supported a significant market capitalization and ultimate acquisition price of $3 billion, despite modest drug sales. In one similar deal that has since created significant value, **Onyx Pharmaceuticals Inc.** (recently acquired by **Amgen Inc.**) partnered the drug platform that produced *Nexavar* (sorafenib) with Bayer in 1994, but retained US co-promotion rights as well as a 50-50 profit-sharing deal abroad (excluding Japan), of which Europe is the primary market. As a result of the 50-50 profit sharing, Onyx is responsible for some of the costs of the launch without the requirement to develop the sales and marketing infrastructure, but it participates in the economic upside.

Despite all the headline and macroeconomic risk, Europe is still an attractive market for novel therapies with convincing efficacy and safety profiles. However, the launch or license decision for European market entry is a major strategic choice, and one with potentially lucrative rewards. For the right companies, a focused and targeted European entry strategy may be the ideal option. And with renewed optimism in the biotech sector, the market might just reward them.

A#2013800207 IV

Robert Easton (reaston@bionest.com) *and Alain Gilbert* (alain@bionest.com) *are co-chairmen of Bionest Partners, based in New York and Paris, respectively; Steven Breazzano* (sbreazzano@bionest.com) *is a consultant with Bionest Partners in New York.*

RELATED READING

"On The Road And Through The Window: Inside Three Biotech IPOs" — *START-UP,* November 2013 [A#2013900217]

ACCESS THESE ARTICLES AT OUR ONLINE STORE
www.ElsevierBI.com

©2013 by Windhover Information Inc., an Elsevier company. No reproduction without the written consent of the copyright owner.