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From collaboration to court

A discussion of "commercially reasonable efforts" in the pharmaceutical industry

In this issue of *CRA Insights,* Dr. Greg Bell, Group Vice President and Global Practice Leader of CRA's Life Sciences Practice, explains how understanding the strategy behind a pharmaceutical product launch can inform contract and licensing agreements.

Background

Research and development in the pharmaceutical industry is a high-cost, high-risk endeavor. Most new chemical entities (NCEs) / new molecular entities (NMEs) that emerge from research labs are expected to fail at some stage of the development process and never make it to market. Of every 5,000 – 10,000 compounds screened at the beginning of the drug discovery process, it is estimated that only one is ultimately approved for commercial sale, and on average only two in ten approved medicines recoup the investment made by companies developing them.[1]

Companies that discover a NCE with the potential for pharmaceutical activity have three primary choices:

- Go it alone,
- Out-license the product with no further involvement (other than as a recipient of milestone payments and royalties), or
- Enter into some form of development or commercialization collaboration.

Given the risks and costs associated with developments and the broad range of activities and capabilities required to successfully commercialize a new pharmaceutical product, collaborations (such as co-development, co-marketing, co-promotion, etc.) are becoming more common. For those firms that decide to collaborate, the complexities and uncertainties of the development process can make it difficult to determine in advance the appropriate time line and activities to be undertaken. Partners often agree to use "best efforts" or "commercially reasonable efforts" requirements to address the difficulty in foreseeing and addressing the possibilities that may arise during NCE development and commercialization. Understanding how those terms are used

[1] PhRMA, "Pharmaceutical Industry Profile 2010," March 2010, pp. 10, 27, http://www.phrma-jp.org/archives/pdf/profile/Profile_2010_FINAL.pdf

in the industry and how commercialization programs are scaled to a potential opportunity may help lessen the possibility of disputes after the ink dries on the collaboration agreement.

Why can it be difficult to define "commercially reasonable efforts?"

GB: The difficulty arises because there is no one single set of activities and efforts that always meets that definition – which is typically why the collaborators used such language to begin with. As with many questions like this, what is "commercially reasonable" depends on the situation and "commercially reasonable" activities and efforts will vary according to the potential opportunity. A commercialization program could be as different as every individual opportunity. Not every drug is a blockbuster and the scale of efforts will depend on the size of the opportunity as well as the specific circumstances of the drug. Is the drug first-in-class? What therapeutic area is it in? What are the company's current strengths and complementary products? All of these factors could affect the development plan. As a result, what constitutes "commercially reasonable efforts" will be specific to the drug opportunity.

Further complicating the process, drug development is a dynamic process. Companies typically adjust and update their plans as necessary to comply with new information and requirements. Development and regulatory approval delays are standard risks for pharmaceutical companies. Understanding the strategic and financial investments required to launch a product can help collaborators develop a realistic commercialization plan for the specific opportunity.

Are there any common elements in developing a launch strategy?

GB: Generally, in preparation for the launch of a new drug product, a company needs to accomplish three goals: build awareness, generate trial, and support usage. In other words, physicians, patients (sometimes), and payors need to be aware of the new product, physicians need to prescribe it, and pharmacists need to dispense it. How those goals should be accomplished is going to depend on the circumstances around a given product and situation. For example, for a drug with a novel therapeutic action, a company will likely want to spend additional resources to build awareness as compared to a drug launching into a well-established therapeutic category with a relatively undifferentiated mechanism of action. Each step along the way requires an investment of time and money – all moving in tandem with the uncertainty about whether or not the drug will actually be launched and with what label and indications.

It would seem timing is everything.

GB: It is important that development and commercialization activities and efforts be appropriately coordinated. There will be uncertainty about when/if the drug will be approved and how that approval will be supported by the results of clinical trials. The choice, breadth, and timing of manufacturing scale-up and launch planning activities can vary, depending on the product and therapeutic category, expectations about approval or marketing authorization date and market potential, as well as a company's own strengths. For example, a company launching a new drug for lung cancer that already has an existing, approved drug and a portfolio of other cancer drugs will have a sales force in place to market the new product. As a result, it may not need to build out its sales force or educate them about the targeted disease – instead it would be sufficient to train their sales force on the details and benefits of the new drug. The expected timing of approval has a significant impact on the timing and coordination of pre-launch activities. For example, market research completed too far in advance of launch may need to be redone to capture market changes closer to the actual launch date. Similarly, a delay in regulatory approval may affect sales forecasts and require an adjustment to pre-launch marketing efforts.

What factors affect timing of launch and a commercialization program?

GB: Regulatory delays are the most common and because the approval process is an ongoing dialogue with the US Food and Drug Administration (FDA), a drug may require additional efficacy or safety testing before approval. The marketplace itself may change with physician preferences for types of treatment evolving which can affect the drug's potential or change expectations for reimbursement. Even in the absence of those volatilities, vicissitudes in clinical trials, data collection, regulatory submission assembly, and related activities often affect expected development timelines. Table 1 contains several types of delays for new drug applications (NDAs) that were approved in 2012, including delays between intended filing date and actual filing date, delayed submission of clinical information, and delays resulting from regulatory responses. For example, Discovery Laboratories received an approvable letter [2] from the FDA for Surfaxin in February 2005. Discovery addressed the FDA concerns and submitted a complete response in October of the same year, adjusting expectation for launch to the second quarter of 2006. However, the FDA subsequently required additional responses from Discovery resulting in further delays in approval and launch of Surfaxin. Discovery ultimately launched Surfaxin in November 2013.

Table 1: New drug applications approved in first half of 2012

Drug name	Intended NDA/BLA filing date(s)	NDA/BLA FDA receipt date	Delay between intended NDA/BLA filing date and FDA receipt date?	Approval date	Launch date	Launch delay (days)
Voraxaze	H2 2005	Jul 18, 2011	Yes	Jan 17, 2012	Apr 30, 2012	104
Picato	Mid calendar-year 2010	Mar 25, 2011	Yes	Jan 23, 2012	Feb 23, 2012	31
Inlyta	2011	Apr 14, 2011	No	Jan 27, 2012	Jan 30, 2012	3
Erivedge	2011	Sep 8, 2011	No	Jan 30, 2012	Feb 2, 2012	3
Kalydeco	H2 2011	Oct 18, 2011	No	Jan 31, 2012	Feb 15, 2012	15
Zioptan	2011	Jan 7, 2011	No	Feb 10, 2012	Feb 23, 2012	13
Surfaxin	Apr-04	Apr 13, 2004	No	Mar 6, 2012	Nov 8, 2013	612
Omontys	Q2 2011	May 28, 2011	No	Mar 27, 2012	Apr 24, 2012	28
Amyvid	2010	Oct 7, 2011	No	Apr 6, 2012	Jun 1, 2012	56
Stendra	H1 2011	Jun 29, 2011	No	Apr 27, 2012	Jan 2014	614
Elelyso	By the end of H1 2009	Apr 26, 2010	Yes	May 1, 2012	May 15, 2012	14
Perjeta	2011	Dec 8, 2011	No	Jun 8, 2012	Jun 8, 2012	0
Belviq	By the end of 2009	Dec 22, 2009	No	Jun 27, 2012	Jun 7, 2013	345
Myrbetriq	Before Mar 31, 2011	Aug 29, 2011	Yes	Jun 28, 2012	Oct 22, 2012	116

Source: CRA research

[2] Beginning in August 11, 2008, the FDA replaced "approvable letters" with "complete response letters." Both were intended to communicate to the applicant what changes were required before the FDA could approve the drug.

So when a dispute arises between the parties to a drug development / commercialization collaboration, how do you determine whether activities were consistent with "commercially reasonable efforts?"

GB: Comparable products—those that have similar commercial potential, are at a similar stage in their lifecycle, or are targeted at the same patient population—can provide a useful benchmark. Costs to develop the product, its proprietary position, the likelihood of regulatory approval, and the competitiveness of alternative products also factor into a determination of "commercially reasonable efforts" which may reflect a range of possibilities that depend on the specific circumstances of the product and the company. In a dispute, examining comparable products helps to determine commercial potential and the range of commercially reasonable efforts. It's unlikely that "commercially reasonable efforts" will lead to one time line of specific activities. If it were easy to define such efforts ex ante, one might expect the parties to have done so in the contract to begin with. In contrast, an assessment of commercially reasonable efforts is likely to be situation-dependent and should be based on the context and information available at the times that the decisions were made and the efforts expended.

That sounds a bit like a way to wriggle out of a contract.

GB: Not at all. Commercially reasonable efforts are based on what would be reasonable for similar products at similar stages in their lifecycles. Here, a key consideration is the size of the expected opportunity and the degree of competition likely to be associated with the opportunity. Obviously, it doesn't make sense to put the same level of effort behind a $1 billion product as it does behind a $250 million product. Similarly, the approach to commercialization for a relatively undifferentiated product in a well-established category facing several competitors is likely to be quite different than the approach that should be taken for a new, first-in-class product that may offer the potential to address a condition in a manner that heretofore would not have been possible.

Gregory K. Bell testifies on commercially reasonable efforts. Recent testimony in a product launch dispute included performing financial and cohort analyses that evaluated the extent and timing of efforts related to the product. Click **here** for more information.

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