

In-Licensing Helps Small Bio-Tech Firms

BY KARE A. TRULL*



In-licensing strategies can be successful, but important issues for study beforehand abound.

Last summer Dura Pharmaceuticals made a Wall Street offering at \$98.75 per share that grossed \$207.2 million for the company. There's a reason that Dura was able to make so much money from the offering: It had several products to sell. But those products weren't the fruit of Dura's R&D. Instead, the company has made a business out of acquiring pharmaceuticals registered by other manufacturers, either approved or in late-stage clinicals, and marketing them.

Over the past couple of years, R&D-based biotech companies have begun to wonder if they can capture a little piece of Dura's magic by in-licensing neglected drugs. The idea is simple: Buy an approved drug that represents less than \$100 million in sales and has a sales force to sell it. The idea is that the big pharmaceutical companies that own such products might consider them negligible and be willing to let them go cheap. Theoretically, the revenues that a small biotech company could get from selling the product would help offset R&D expenses and give it a chance to develop and gain a sales force while waiting for approval of its own products.

It's more than just a theory. Several companies have used this strategy successfully. But companies wishing to pursue this approach have to consider a few important issues before they go on a shopping spree.

ARE THEY REALLY OUT THERE?

According to Robertson Stephens & Co. Institutional Research, 80% of the revenues from the 162 billion

U.S. pharmaceutical market come from individual drugs with annual sales of \$50 million or less. That makes for a lot of small products.

"Obviously they're not in all therapeutic areas and they're not all available for in-licensing or acquisition," says Alex Zouros, an analyst with Hambrecht & Quist. "But up until now, there have been enough to go around."

"Big pharma and even mid-sized pharma have a lot of stuff on the shelves that, for a variety of reasons, kind of falls through the cracks," agrees Victor Lee, head of Veeva Lee and Associates, a consulting firm based in New York City. "In a certain percentage of the cases, it's because the product is a dud no matter what. But I think there is a fair proportion of cases where the product is fine or it's reasonably developable, but it couldn't fit into the manufacturer's budget or for political, strategic, or market reasons." Lee also observes that there are drugs that are being marketed or developed for only one indication by their owners, leaving other indications open to acquisition.

In fact, this may be the ideal in-licensing scenario. Novus Corp. of Menlo Park, California, for example, is hoping to grow up its marketing operations by selling Carbagene, a drug that once received a "not approvable" letter from FDA.

The drug, an IV formulation of fenoldopam, was developed by SmithKline Beecham to treat malignant hypertension, a rare form of hypertension found in about 10,000 U.S. patients per year, according to Novus chairman and CEO Paul Goodland, Ph.D. SmithKline submitted an NDA for the IV formulation of the drug in 1989, followed by data to support an oral formulation of the drug. When the

oral version was determined to be unapprovable because of bioavailability problems, SmithKline dropped development of the drug altogether.

Novus purchased rights to the drug from SmithKline in May 1994 for about \$1.5 million. Rather than simply address the problems that led to SmithKline's rejection, however, the company decided to pursue a broader range of indications. The company resubmitted the NDA last June, but for a new indication: control of blood pressure during surgery, particularly cardiac surgery, where oral drugs are impractical or otherwise contraindicated. Goodland believes that the cardiac surgery indication represents about 450,000 patients annually, with general surgery representing a further 300,000. What's more, Novus hopes to get Colgospin approved for use in surgery "where maintenance or improvement of renal function is considered to be important."

This language, the company hopes, will lead the way for a broader market of blood pressure control in acute renal failure patients — a further 300,000 patients a year that the company hopes to address with a pending formulation of Colgospin now in development.

Goodland estimates that Novus spent \$5 to \$9 million developing Colgospin after acquiring it from SmithKline Beecham, and says that analysts have predicted annual sales for the drug, once approved, of \$40 to \$60 million per year.

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At present the FDA is under FDA review and has not yet been scheduled for an advisory committee meeting, so it's too soon to say if Novartis' strategy will prove to be as clever as it sounds. But if it all goes well for the company, it could increase sales of Celecoxib 10-fold over SmithKline's original market.

CHOOSING THE RIGHT PRODUCT

Goldman emphasizes that the acquisition of Celecoxib was part of a deliberate strategy to prepare the company for marketing its own R&D product, SMO-111, for a severe pain indication. "SMO-111 is an important product for us," Goldman said. "It's on our teeth on it [in the marketplace] is very dangerous. We can't afford to get it wrong." Instead, Novartis plans to get a sales force of about 20 people that will concentrate on selling Celecoxib in about 600 major centers, hoping to reach the same rheumatologists and other prescribers who will be customers for SMO-111 in the future.

"You can figure it out yourself," says Goldman. "That's about \$6 million for the sales force, say another \$6 million for sales and marketing costs, and maybe \$5 million for Phase IV studies and cost of product. If sales are \$50 million a year, a lot of the revenues will go straight to the company." Novartis is projecting a net loss of \$25 million for this year, but Goldman hopes Celecoxib will go a long way toward offsetting future losses.

When he made the decision to acquire the drug, Goldman also considered Celecoxib to have a "moderate potential" that originally pursued by SmithKline Beecham. "I would not have done it if I didn't believe that."

"That's the trick for companies like us — to expand the profile of in-licensed drugs," Goldman adds that he is interested in "very selectively" in-licensing other products. He says he will wait until he receives an appreciable letter or a favorable advisory committee hearing before hiring sales reps.

Of course, this strategy only works if you find the right product.

Andrew Becker, executive vice president of the Mendel Group, a Redwood City, California-based consulting group, says that "there are lots of radiology drugs available," but points out that "most companies with a \$20 to \$50 million oncology drug won't become there."

So how do you find the perfect product? Becker says that the "best way is to have a relationship with the business development executives at big pharma." This can amount to simply increasing your chances of being in the right place at the right time. Goldman had a leg up including Celecoxib — he came to Novartis from SmithKline, where he was involved with the product. Tom Wiggins, president and CEO of Connective Therapeutics in Palo Alto, California, says that one of his company's in-licensed products, a benzimidazole molecule to treat osteoporosis and psoriasis, was identified by the company during a change-on-the-spot meeting between a Connective employee and an old friend at Medeva, the company from which Connective acquired the molecule.

"You don't just have to count on luck. Becker notes that there are a variety of databases keeping track of information on products, their sales levels, and whether they are being developed.

DO'S AND DON'TS OF IN-LICENSING

Even if a company is in-licensing a product as a marketing platform for its R&D pipeline, it must determine whether to pursue approved products or late-stage developmental products.

"It's obviously much lower risk to get drugs that are on the market, because everybody knows what you're dealing with," says H&Q's Zanon, who has championed the in-licensing strategy. "It's sometimes harder for Wall Street to evaluate drugs that have been buried in Phase II trials in big companies, and there's always some suspicion that, if the product is really so good, why is the company out-licensing it?"

"If a small company is close to

selling its own drug, then it makes much more sense to target drugs that are already on the market," he continues. "Because it gives you some leverage for your sales force. Whereas if you're close to making money on your internal operations and you go out and acquire a bunch of drugs in Phase II or Phase III, there's all of a sudden your R&D costs are going to go up, and you probably won't be profitable over the next year or two. And Wall Street generally will not look upon that very favorably. They are geared to expect profitability."

Still, companies that gamble on earlier-stage products can often acquire drugs for a song, as was the case with Celecoxib or Connective's benzimidazole molecule, acquired for about \$100,000 plus royalties. If you are in the market for an approved product, says Zanon, expect to pay anywhere from one to three-and-a-half times sales for it.

This is exactly what Connective did with a most recent acquisition. Bichem, a SmithKline Beecham drug to treat rheumatoid arthritis. Connective paid \$25 million for the drug (which includes a royalty agreement with a lifetime cap of \$6 million). 1999 sales of the drug, Wiggins says, were about \$10 million. The drug fits into the company's overall in-licensing strategy, he says, in that it can be marketed to the same customers that Connective eventually hopes to reach with its earlier-stage products.

Although all of the products in Connective's pipeline were in-licensed from other companies, Wiggins tells the company was ready to acquire its first approved product because its development product was getting close to market (he hopes to launch CPO-011 in late 1999 or early 2000). "It doesn't make sense to do this if your R&D products aren't close to market."

In-licensing products that mesh with your pipeline is vital, says Zanon, "unless it is the first step in a strategy to become a big player in that area." Otherwise, "it's a big red flag, because the key to the strategy is that you're trying to take advantage of fixed costs, meaning a sales force. And if every time you

get a new product you have to expect your sales there, it's more of a Ford scheme."¹

CAVEAT EMPYOR

Clash Casanueva, president and CEO of BiBoGene Inc. of Hayward, California, has had mixed experiences with in-licensing. When Casanueva was CEO of Intermune Pharmaceuticals, he was the chief force behind the in-licensing of celecoxib (Celebrex), the obesity drug that has since been resold to American Home Products and is now marketed as Roflum. In that case, the strategy gave Intermune a quick way to make some money and bolstered its ability to raise capital. Clinical trials supporting European approval had already been conducted by Biexin Laboratories SA, the French company that originally developed the drug. Intermune was able to in-license the product with some confidence about its efficacy and conduct the trials necessary for U.S. approval.

At BiBoGene, Casanueva decided to repeat this strategy by seeking late-stage products that the company could put on the market and use to support R&D. The products included a usually administered anti-emetic called ondansetron, which was in Phase III development at Hyline Laboratories Inc. The company was hoping for a quick approval and a chance to bring in some income, but it discovered that getting the data to support an NDA was more difficult than it had anticipated.

Casanueva acknowledges that he was looking for products that could quickly bring in sales revenue, rather than trying to find products that would mesh with BiBoGene's R&D pipeline.

"What I learned from the process is that you really need the resources," Casanueva said. "Even if you acquire a product with a lot of clinical data behind it and good market potential, he says, "it still going to require some \$6 to \$8 million to get the first NDA submitted, and then to set up a marketing and sales organization will take more millions. It was probably too early to do that for a private com-

pany that had about \$8 million in the bank."

BiBoGene, says Casanueva, has decided to concentrate on its proprietary R&D. NDAs for celecoxib have been submitted in Spain and Italy through licenses, which Casanueva hopes will bring in some royalty revenue down the road.

In the meantime, BiBoGene is concentrating on its anti-obesity research program, which is being funded by Abbott Laboratories. That program, aimed at the discovery of a new anti-obesity via transcriptional control gene repression, had led to several lead compounds that should enter animal trials this year.

HOW DO IT AGAIN?

One thing that companies interested in in-licensing drugs often fail to consider, Michael Group's Becker says, is their sales force. On paper it may make sense to acquire a drug with established sales links and profitable profits, and then sit back and let the money roll in while waiting several years for the R&D pipeline to reach the market.

But, as Becker puts it, "sales people get bored pretty easily, so you have to keep adding things to the bag — otherwise, they'll leave."

In other words, companies should think carefully before undertaking in-licensing as a one-time strategy. "It's great to have revenues, and Wall Street loves companies that are in-licensing products," says Becker, "but you have to consider how you will keep your sales force happy. Incentives are built around growing sales — if sales are flat, the sales people won't have much incentive to sell and will look for other opportunity. If they have to sell this product while waiting three years for an approval of an R&D product, they probably won't stick around."

Companies should therefore plan on acquiring more than one product unless approved for an in-house product in truly imminent. And there's another reason to adopt this strategy: You never know for sure if a product will be approved and it actually is. One in-licensing

product may not a contingency plan make, but several in-licensing products may help support a company through an anticipated repeat Phase III trial, or even represent an entirely new business plan.

Genzia Inc. found itself in the latter position after the failure of its adenovirus regulating drug, and it has gone on to make a business out of paper NDAs and in-licensing devices. Genzia purchased Kendall McKine Laboratories, a generic manufacturer, as a contingency strategy, and may still months survive to this full-back plan. In late February the company acquired three new specialty pharmaceutical companies.

Cytos Pharmaceuticals in San Diego, California, has approached in-licensing as an iterative cycle. The company is currently marketing three products: Glaxo 123 and Immit, two products for assisting glomerular filtration rates that were acquired from Bio-Tec (Dagupan, Inc.; Princeton, Texas), in August 1995; and rhobovine, its first upper GI bleeding, which was acquired November 1996 from Schwann Pharma AG.

According to Larry Blum, director of sales and marketing at Cytos, rhobovine was just "sitting on the shelf" at Schwann Pharma, not being promoted. Annual sales were about \$1.2 million when Cytos acquired it (but about three times sales) for hopes to increase sales by about 300%.

The company currently has six sales reps, says Blum, and hopes to have 10 by next year. By the time Cytos launches its own R&D products, which he hopes will happen in the next two to three years, Blum would like to have a sales force of 20 to 30 people selling not only the company's three current products but several other in-licensing products that the company is now "actively pursuing."

Blum points out that in-licensing has its own momentum, because a company that is already selling something is more likely to have both the money and the infrastructure to effectively acquire and launch other products. This "puts the company in a position to be opportunistic," he says.