Looking for value

In developing next-generation technology platforms, many biotech companies have forgotten to generate equity.

BY RANDALL C. WILLIS

Discussions about creating an integrated path for drug discovery are becoming all too common as researchers and company executives struggle to channel technological advances toward product development goals. Steven Holtzman, president and CEO of Infinity Pharmaceuticals, found he wanted to add something new to the dialogue as the keynote speaker at the recent Bio-IT World Conference in Boston. To focus on the larger context, Holtzman argued that the real challenge the drug discovery field faces is not just integration but actual value creation. His perspective comes from many years' experience in the biotech industry, including having been Millennium Pharmaceuticals' chief business officer and the founder of DNX Corp.

The 1990s witnessed a biological revolution as advances in fields such as genomics, proteomics, and high-throughput screening pushed the boundaries of medicinable molecular space. This shift offered drug discovery scientists potential access to all human genes and proteins, and a clearer understanding of how their functions interrelated. These scientists could then screen vast numbers of compounds against a great variety of targets, generating large quantities of data. So the question remains: Has this technological revolution led to an equivalent revolution in drug discovery products? Unfortunately, Holtzman believes, the answer is no.

"Technology that is important and enabling may not be enough in itself to create value," Holtzman explained, arguing that too many companies tend to focus on developing technology platforms without giving sufficient thought to how they will be able to translate these advances into a valuable commodity or product.

What went wrong?

Part of the challenge facing newer drug discovery companies, Holtzman argues, is that although the new technologies allow researchers to screen a greater number of targets, many weakly validated targets make it into the clinic, where they fail, in some cases because they are not medically relevant. Alternatively, of the thousands of possible targets, many have been classified as intractable, inaccessible, or not druggable, and therefore, he believes, many potentially important, biologically well-validated targets have been excluded from consideration.

Another challenge is that there has not been a chemical revolution to match the biological revolution. Although advances in combinatorial chemistry have produced more massive libraries of compounds, these collections exhibit little chemical diversity.

PHOTO: INFINITY PHARMACEUTICALS

Holtzman

"More complex molecules, with biologically active and selective stereochemistries, are not being produced," he said. "Hence, the increased number of compounds does not truly provide more distinct drug candidates."

In the long run, the situation becomes the chemical equivalent of trying to talk to someone who doesn't speak your language: Simply talking louder but using the same words will not make your message any clearer.

Holtzman also believes that although IT innovations are key to biotechnology-driven drug discovery, they are only incrementally so, and the success of any initiative will depend largely on the facile integration of third-party tools and transparent organization-wide access to data and thinking. He suggests people should "focus on information that would have an impact on decisions critical to value creation," but he warns that this step implies a willingness to fail openly.

Creating value

According to Holtzman, value creation in biotechnology is all about the product—namely, important new medicines. But to get to this point, he believes the ability to develop value-accretive financing that will allow scientists to fail often enough to eventually succeed is almost equally critical. He is very specific, however, in how he defines biotech companies.

"These are companies that begin with fundamental new life science technologies and propose, from such a starting point, to create enterprises that discover, develop, and eventually market new medicines," he explained. Thus, he does not include research tool companies, service providers, or pharmaceutical company spin-offs with mature drug pipelines.

Holtzman examined the product and financial histories of 14 of the top biotech companies including leaders such as Vertex Pharmaceuticals, Genentech, and Gilead Sciences. He noted that although it took an average of nine years for these companies to commercialize their first products, each one quickly had its first molecular entity into humans and began to show a profit within five to seven years. Equally important, he added, was that all of them had developed product pipelines; there were no one-drug wonders.

A key component to the success of these first-generation companies, Holtzman argues, was their focus on developing products in a manner totally different from the pharmaceutical firms that predated them. For example, recombinant DNA technologies allowed biotech companies to develop products such as human insulin in low-cost, high-yield bacteria; monoclonal antibodies allowed companies to target cells more specifically; and early genomics efforts allowed companies to increase drug efficacy.

Newer biotech companies, however, will not have it so easy. To succeed in the marketplace, he suggests, the next-generation

companies will have to not only develop better drugs than the incumbents but also develop drugs better. And to be better, they will need cash from nonequity sources.

Money, money, money

According to Holtzman, components for success include a diversified product portfolio that will limit developmental and financial risks, a broad technology platform that creates multiple product opportunities, and value-accretive financing. A successful biotech company can expect to spend $750 million to $1.5 billion within its first decade of operation, and traditionally, this money has come from one or more of four sources:

- income-generating partnerships,
- financial engineering,
- bubble markets, and
- big-brother agreements and mergers or acquisitions.

For the next generation of start-ups, however, many of these options might be closed.

Pharmaceutical companies are "still digesting their large platform investments of the 1990s," Holtzman said, and mergers between the larger firms have reduced the playing field. These companies are also experiencing increased pressure for earnings growth and therefore are focusing their efforts on late-stage pipeline development. Similarly, the financial engineering common a decade ago—through mechanisms such as R&D-limited partnerships and special-purpose accelerated R&D corporations (SPARCs)—has all but dried up in the post-Enron, post-Elan world.

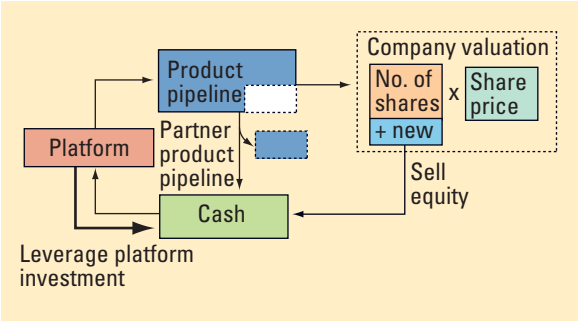
The dot-com crash has led to reduced consumer confidence and the flight of money to safer investment instruments, such as mutual funds. Likewise, the creation of monster funds has moved money away from smaller capital investments. Fund managers, Holtzman argues, would rather execute ten $50–100 million investments than 100 $5 million investments.

Big-brother partnerships and acquisitions have proved successful for some companies—for example, Chiron with Ciba-Geigy and Immunex with American Cyanamid—but, in many cases, it is taking longer than desired for pipelines to come to fruition, and money spent investing in pipeline development is money lost from earnings.

A matter of leverage

Holtzman diagrammed the funding dilemma and offered a possible solution. To raise funds, some company executives may decide to sell equity in the form of new shares, but this process dilutes share value and can make a company less attractive to investors. Alternatively, a company can partner or sell part of its product pipeline to another firm, but, according to Holtzman, this can be a recipe for disaster because the seller loses a valuable commodity and potentially mortgages its future.

Rather than dilute a company's chances for success, Holtzman argues that management should find ways of raising funds by doing what it does best: It should leverage technology platforms. This would allow other companies to reap the benefits of these innovations for a price. Genentech used this process successfully, and it is a significant mechanism by which Infinity Pharmaceuticals raises capital.



Leveraging platform investments can be key to the biotech start-up value creation cycle. (Figure courtesy of Infinity Pharmaceuticals.)

Although start-ups face a more expensive and challenging financial and partnership environment, Holtzman believes the fundamentals of success remain the same. A company should offer the best people innovative and transparent work environments and communication. It should stay product-focused but build technology platforms that it can use to generate its own products as well as bring in cash to invest in its own pipeline. And it should discover and develop better medicines.

"If you do that, and you're smart, and you're very lucky," Holtzman jested, "you have a very slim chance of succeeding." ■