

# Discovering the potential of drug discovery

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▼ Most will agree that this past year has not been a kind one to companies both big and small. With the demise of 'dot-coms', the shrinking of the Nasdaq stock market and the close of the initial public offering (IPO) window, one might think that it is an especially tough time for young start-up companies. Nevertheless, biotech venture capitalists have raised funds of more than US\$400 million so far in 2001, with a few firms closing in on funds approaching US\$1 billion. In the first three-quarters of 2001, US\$1.6 billion of private equity and venture capital was invested in 147 pre-public biopharmaceutical companies (VentureOne Database, San Francisco, CA, USA; <http://www.ventureone.com>). Although later-stage biotech might have to tap into these larger funds for an additional funding round while waiting to go public, early stage companies are betting that by starting today, they will be in a good position for the next cycle when the market heats up again. Overall, the sentiment in biotech is one of growth and optimism, as opposed to one of conservatism and defense. Underlying this sanguinity is the fundamental attraction of the drug discovery industry.

## Why is the industry attractive?

The business of drug discovery pays out handsomely – for those who can play it right and manage the risks. Gross margins for the pharmaceutical industry rival the software industry at 80–90%, while the productivity and competitive positions of the large incumbent pharmaceutical companies is actually declining. Despite advances in high-throughput technologies, such as genomics, combinatorial chemistry and HTS, and enormous jumps in annual worldwide ethical drug R&D spending from US\$2 billion in 1980 to US\$10 billion in 1990 to over US\$30 billion in 2001 [1], the number of new molecular entities (NMEs) produced by the industry each year has remained relatively constant. To date, the industry has been able to justify this apparent gap between input dollars and output NMEs because sales of blockbuster drugs have tempered the rise in R&D spend as a percentage of

sales. But this is a vicious cycle – the less productive the drug discovery process becomes, the greater the reliance on blockbuster drugs. What if the drug discovery process was more efficient? In an industry thirsty for new technology and laden with the as yet unrealized promises of earlier technology investments, what are the challenges and opportunities for new entrants?

## Bar to success

Although the bar to become a successful start-up is high, many of the stepladders necessary for overcoming this bar are already in place. A decade of intensive investment in high-throughput methodologies has created powerful techniques and methodologies whose full value has yet to be realized. Combinatorial chemistry and genomics are two cases in point. Combinatorial chemistry has matured to a point at which many thousands of molecules can now be routinely generated. Although it is conceivable that such a technique could make small molecule libraries faster, cheaper and better, experience to date suggests that it creates greater numbers of cheaper molecules, but the molecules themselves are not necessarily better. The result: pushing greater numbers of potential failures further into the clinic. Therefore, although the infrastructure for combinatorial chemistry has been built, might a subtle change in approach also create better molecules and thereby unlock the potential for enormous value?

The genomic revolution has also created an infrastructure with a potential ready to be realized. Whereas sequencing of the human genome expanded the number of potential drug targets, it said nothing about the validity for drug development of individual targets. Is there room for a start-up to better utilize the information from the genome? Computational power has been growing exponentially in the past decade; can the power of supercomputing finally be applied to *in silico* lead discovery? Also, advances in miniaturization science now enable experiments to be carried out on a new scale: so, are new methods of drug discovery enabling higher productivity? These are but

a few of the tools already in place for biotech start-up companies attempting to clear the bar of success.

The challenge in clearing the bar, of course, resides in proof of productivity enhancement. Companies must be able to demonstrate how (increased probability of success, reduced time and reduced cost) and where in the drug discovery value chain productivity improvements are to be realized. A particular challenge to early-stage companies is the fact that the largest value to be captured resides in innovations that affect the later stages of drug development, thus improving the probability of success of clinical trials. However, such improvements only manifest themselves many years later.

### Avoiding the pitfalls

Drug discovery biotechnology companies that can convincingly demonstrate their productivity value proposition will be the partners of choice for pharmaceutical incumbents. Here, the challenge for the discovery start-up is to ensure that its platform is of sufficient breadth (applicable to more than one drug or class of drugs) and value, so that it can keep a portion of the platform for internal discovery efforts while using the remainder to raise capital through pharmaceutical partnerships. A common pitfall for many biotech start-ups is that their platform is not sufficiently broad, and as a result they are unable to raise sufficient capital, and thus also unable to diversify their own risk through a portfolio of projects. The common outcome of such a scenario is one in which the company bets its future on one lead project. All too often, when the lead project fails so too does the company. Raising sufficient capital is important because it enables a start-up to pursue more than one line of development, and raising the capital from pharmaceutical partners is key in minimizing share dilution and generating shareholder value.

An alternative way to play the biotech start-up game is to be a technology provider that does not undertake internal drug discovery. The challenge for platform technologists is to stay ahead of the technology obsolescence curve. They must either continuously invest in R&D to remain at the forefront of technology, or build a technology standard that has both a long shelf-life as well as barriers to competitive entry.

What might be a unique and competitive technology today may well be a broadly available commodity tomorrow.

Although technologically and operationally challenging, less risk and less capital are typically required to build platform tool companies. Such technology platform companies are attractive to many investors because of the prospect of near-term revenues and earnings. Requiring less risk capital and presenting a lower overall risk profile, platform technology companies are able to more tangibly demonstrate their value at an earlier stage. However, the near-term advantages must be considered against the long-term implications. The lion's share of the rewards in drug discovery are bestowed upon the drug discoverers themselves, and platform technology companies must recognize and accept early on that they are, and will be, on a different (lower) long-term valuation trajectory. A common mistake and temptation is to attempt a transition from being a technologist to a drug discoverer – the culture and infrastructure are significantly different and few companies have successfully undergone this awkward transformation. The bottom line is that you can succeed as either a drug discoverer or as a platform technology provider. What will prove fatal is a failure to decide and know which you are.

### Concluding remarks

The past year has seen the growth of both drug discovery and platform technology start-up companies. In many respects, their timing may well be perfect. Now, more than ever before, the industry is in need of new and more-efficient ways of discovering drugs. Combined with the yet-to-mature fruits of years of high-throughput research waiting to be harvested and the availability of venture capital, a unique environment is in place to support these new companies. Those companies that can demonstrate their ability to increase drug discovery productivity, whether as platform providers or as drug discoverers, will be welcomed by both pharmaceutical and larger biotech companies alike.

### Reference

- 1 PhRMA Annual Survey (2001) Parexel's Pharmaceutical R&D Statistical Sourcebook (Methieu, M.P., ed.), Parexel International Corporation