# In vogue with venture

Gary Patou

**What types of life science enterprises are attracting venture capitalists today?**



The current financial and regulatory environment is posing challenges to investors and entrepreneurs in the healthcare sector. Fewer dollars are going into venture capital and fewer venture capital companies have money to invest. There is a dearth of pharmaceutical acquisitions, the traditional exit for healthcare investors. The pace of pharmaceutical deals has slowed, and the deals that are getting done are often structured buyouts (**Box 1**). Although initial public offerings have been happening, only a select few companies have attained expected valuations. Coupled with political pressure to emphasize drug safety and ever more stringent regulatory hurdles, life science enterprises are faced with several challenges due to the current market environment.

Yet big pharma continues to require assets from biotech to fill both its ever-increasing development pipeline deficit and the gap in their offerings as products face patent expiry. What's more, first-round biotech pre-money valuations are lower than ever—an average of $3 million last year compared with an average of $21 million between 2005 and 2009—enticing more investors into doing deals.

So what are some of the key criteria that these venture capitalists (VCs) are looking for in a potential business?

## Innovation is highly prized

Several pharmaceutical companies have restated their commitment to bringing forward innovative, first-in-class products. With a more capitally constrained pharmaceutical industry and sophisticated marketplace, it is hard to justify fast followers, especially in indications for which there is the potential of several entrants competing for a finite market with limited differentiation. Markets that traditionally have sustained multiple entrants (for example, the hypertensive drug classes, beta blockers, angiotensin-converting enzyme (ACE) inhibitors and classes of antibiotics such as cephalosporins) are not doing so with newer drug classes; thus, innovative first-in-class therapeutics are highly attractive.

Biotech companies that bring the promise of new therapies through proprietary new targets and new biological pathways are highly attractive to big pharma and, consequently, to the investment community. There have been two recent examples of attractive exits for innovative companies. The first is Calistoga Pharmaceuticals (Seattle), which was purchased by Gilead (Foster City, California) for $375 million upfront and an additional $225 million in potential milestone payments. Calistoga was bought for its highly innovative phosphatidyl inositol 3-kinase (PI3K) inhibitor program in oncology. The second example is Plexxikon (Berkeley, California), which was acquired by Daiichi Sankyo (Tokyo) for $805 million upfront and $130 million in potential milestone payments. Plexxikon had a first-in-class oral small molecule BRAF inhibitor for melanoma. Both of these buyouts show there is a market for companies working on new therapeutics.

At the other end of the spectrum, MPM Capital (San Francisco) was invited to invest in a company developing a new dipeptidyl peptidase 4 (DPP4) inhibitor for type 2 diabetes. The compound looked to be safe and efficacious from the phase 2 trial results. However, it was barely differentiated from Merck's (Whitehouse Station, New Jersey) Januvia (sitagliptin) and AstraZeneca's (London) and Bristol-Myers Squibb's (Princeton, New Jersey) Onglyza (saxagliptin). The company had a partnership already announced with a specialty pharmaceutical company, but MPM was concerned that the partnership might dissolve, as the phase 3 trial costs loomed. That would have required the venture investors to fund the trials, and diabetes products require large, expensive studies.

Thus, this compound failed to meet our innovation criteria, and MPM passed on funding. The company subsequently lost its commercial specialty pharmaceutical partner and faced the prospect of funding its own phase 3 studies. It could not find investors willing to take this bet. The company had a perfectly good drug, but in today's world the bar is set higher and the compound was insufficiently differentiated to attract the interest of big pharma. Even five years ago, it's likely many major pharmaceutical companies would have seen the value in building a diabetes franchise, and even a modestly differentiated new entrant, such as this, would have been of interest to several of them.

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### Box 1 Buying in tiers

Structured buyouts are a way for investors to hedge against risk. A good example is Cubist's (Lexington, Massachusetts) buyout of Calixa (Lexington) in late 2009. Cubist sells the antibiotic Cubicin (daptomycin) and was interested in Calixa's lead compound, CXA-201, an intravenous combination of a cephalosporin (CXA-101) and a β-lactamase inhibitor (tazobactam) being developed against Gram-negative bacterial infections.

The purchase called for an upfront payout of $92.5 million in cash, making Calixa a wholly owned subsidiary of Cubist. But Cubist is also responsible for potentially making payments of up to $310 million to Calixa stockholders for the achievement of certain development, regulatory and commercial milestones for products that incorporate CXA-101.

### Adopting orphans

The popularity of orphan drugs is growing in the current regulatory environment. Often the unmet medical need is high in these diseases. Consequently, regulatory authorities tend to take a pragmatic approach to orphan drug development. Orphan diseases often have monogenetic origins, with less complex biology that tends to be amenable to interventions that are often highly effective. The clinical trials usually require fewer participants than trials for nonorphan indications, if the treatment effect is large. In addition, the pool of available patients for study is small, and the lack of feasibility to recruit large participant numbers in an orphan setting is recognized by the regulatory authorities.

This all makes it more affordable for VCs to finance these drugs. Highly effective treatments often garner higher prices. Examples would be Gleevec (imatinib), which was first approved for chronic myelogenous leukemia and sold about $4.3 billion worldwide for Novartis (Basel, Switzerland) in 2010, and Cerezyme (imiglucerase), the enzyme-replacement therapy for Gaucher's disease that sold $1.2 billion for Genzyme (Cambridge, Massachusetts) in 2008 (manufacturing issues dropped supply in the following years).

Drugs designated for fast-track review by the US Food and Drug Administration, which is often the case for orphan disease products, have a 50% probability of first-time approval, compared with 20% for nonpriority drugs. The sales and marketing costs for orphan indications are modest compared with those for other pharmaceutical products, and so it is highly cost efficient to realize the value of a product in this category. GlaxoSmithKline (Brentford, UK), Novartis, Pfizer (New York) and Lilly (Indianapolis) all have announced major initiatives in house for R&D into rare diseases and thus should be looking to buy programs and companies.

MPM recently invested in a company developing an orphan drug for pancreatic insufficiency in cystic fibrosis patients. The company, Alnara (Cambridge, Massachusetts), had developed the synthetic, non–animal-derived pancreatic enzyme-replacement therapy Solpura (liprotamase). The current standard of care is a porcine-derived product that carries a high pill burden and a growing safety concern following the problems with porcine-derived heparin. The product had completed phase 3 trials and was quickly acquired by Lilly before approval for $180 million upfront and $200 million in potential milestones.

The Alnara purchase highlights the desirability of orphan products by big pharma, and thus they are of interest to VCs, too. Still, even with the orphan indication, it's useful to note that our over-riding interest in the company was for the core technology itself.

### Advantages to biobetters

For some years now, both traditional small molecule–centric and large specialty pharmaceutical companies have been signaling strategic interest in biologics and have purchased biologics companies. For example, Merck has acquired Glycofi (Lebanon, New Hampshire) and Abmaxis (Santa Clara, California); AstraZeneca bought Cambridge Antibody Technology (Cambridge, UK) and MedImmune (Gaithersburg, Maryland); Bristol-Myers Squibb snapped up Medarex (Princeton, New Jersey); and Cephalon (Frazer, Pennsylvania) swallowed Arana Therapeutics (Macquarie Park, Australia) and Ception Therapeutics (Frazer). This trend is likely to continue, and it makes next- or second-generation biologics platforms a hot area for investment in the coming years.

These platforms seek to engineer improved efficacy, dosing convenience or pharmaceutic properties with modifications, in particular to the Fc portion of antibodies or by generating bispecific antibodies that bind two different antigens. It means big pharma is interested in not only buying these platforms, but also partnering with the companies behind them. For instance in 2010, Boehringer Ingelheim (Ingelheim, Germany) formed partnerships with both MacroGenics (Rockville, Maryland) and F-star (Vienna, Austria) for next-generation antibody therapeutics, putting a combined potential total of nearly $3.9 billion on the line between the two partnerships. It's unlikely those deals will pay out in full, and acquisitions better highlight the general interests of big pharma, but the deals are notable.

### Success breeds success

The success and experience of company management is a critical factor in the likelihood of future success of a startup. Drug discovery and development is fraught with obstacles and 'curve balls'. These are often unknowable at the time of investment. A high-performing team is more likely to navigate these challenges or create new opportunities. Success begets success.

MPM recently invested in a preclinical stage anti-infective company in which six VCs competed to participate. A large part of the attractiveness of this deal was the track record of the team, which had successfully sold three prior anti-infective companies in the past six years for several hundred million dollars. That sort of track record leads investors to believe a similar outcome is likely. If you don't have that type of experience on board, go out and seek it.

### Plan ahead

It is important that companies establish target product profiles and credible, cost-effective, comprehensive development plans through key inflection points that derisk their assets. You also need to demonstrate likely exit points through trade sales to big pharma.

### Comparative effectiveness

Attention to differentiation from both in-class and other therapies directed to the same indication are increasingly critical. Though this has clearly always been important for the successful marketing of drugs, it has now evolved into the concept of comparative effectiveness—the ability to demonstrate clinically the value proposition for a new drug over standard of care. The ability to benchmark a new drug over an existing, approved product for the same indication is a requirement for European drug development and approval, and the demonstration of superior cost effectiveness is a requirement for drug reimbursement in the UK, determined by the National Institute for Health and Clinical Excellence. Comparative effectiveness is increasingly important in the US for managed care decisions regarding drug reimbursement—at what price and at what preferred tier status—and for hospital formulary committee acceptance of new products.

The new Patient-Centered Outcomes Research Institute (Washington, DC) has been funded with $1.1 billion by the US government and is likely to affect reimbursement decisions by US government–supported health plans. All of these trends underscore the importance of considering how your company will demonstrate comparative effectiveness for your product, at some level, ideally in trials before drug approval. Managed care companies are remarkably approachable and willing to enter these discussions even before drugs have reached approval.

As VCs focus on their companies' customers and potential acquirers, comparative effectiveness is increasingly part of their consideration of the product's attractiveness. Biotech management teams that tackle these questions early help potential investors get comfortable with the commercial attractiveness of their assets.

### Capital efficiency

There are a growing number of sources for nondilutive capital: specific disease

interest groups, such as the Cystic Fibrosis Foundation (Bethesda, Maryland); developing world charities, such as the Bill and Melinda Gates Foundation (Seattle); government programs, such as the Department of Defense's Project BioShield; and various state initiatives (Texas, Kansas and Florida all have active initiatives to attract biotech businesses).

It is highly desirable for biotech companies to reduce the financing burden on venture equity investors by accessing these funds, if possible. But just having the aspiration for grants is not compelling enough to investors. It is critical to have attracted these funds before you start knocking on investors' doors.

## Evolve or die

These are difficult times for entrepreneurs attempting to commercialize discoveries out of academia. Over the past few years, healthcare investment has increasingly migrated away from academic discovery to firms already bringing in money. The latter have not been the traditional staple of VCs; they have more typically been the purview of hedge funds and private equity. With the contraction of public funding sources and the reduction in valuations of even revenue-generating companies, VCs are migrating to these companies because of their limited regulatory risks and are playing the arbitrage between depressed price-to-earnings values and growing revenues.

The upside is that the present time is one of the best opportunities for investing risk capital because valuations are so low. That is as true in health care as in other sectors. The sage of Omaha, Warren Buffett, recently commented while observing the turmoil in Japan following the tsunami, "This is a buying opportunity." So if you have a startup that meets some, if not all, of the above criteria for attractive investment opportunities, then your pitch might not fall on deaf ears.