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Trendspotting: betting strong but playing safe

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An analysis of recent trends in licensing and financing transactions that affect early to mid-stage life science companies and their investors.

Since the beginning of 2005 and into this year, we have observed several trends impacting early to mid-stage life science companies in the areas of financing, licensing and collaborations, and intellectual property. Last month, we focused on intellectual property. In part two, we analyze trends in financing and licensing transactions, many of which appear to be related to each other, or the natural consequences of larger trends. For example, the growing size of early-stage venture financing transactions appears to result from decreased access to the public markets for the funding of early clinical development. Similarly, the reemergence of early-stage corporate collaborations appears as the natural consequence of the flurry of activity in later-stage collaborations over the past several years. In addition to the changing dynamics of collaborations and fund-raising levels and valuations, we look at who is getting financed.

Pharma's return to early-stage deals

One notable trend is the resurgence in the number and size of licensing and collaboration transactions for therapeutic compounds in preclinical or early clinical development, which is good news for early to mid-stage companies and the venture capitalists who invest in them. For example, last year Piramed of Slough, UK signed a deal with Genentech for preclinical-stage cancer compounds valued at $230 million, not including royalties. In another oncology deal, Coley Pharmaceutical Group of Wellesley, Massachusetts, licensed ProMune (CPG 7909), a toll-like receptor 9 agonist in phase 2 clinicals, to Pfizer, with an initial payment of $50 million and the potential for up to $455 million in additional milestone payments plus royalties. Although pharmaceutical companies' need to fill dwindling product pipelines is hardly a recent trend, the industry now appears concerned that most of the low-hanging fruit in later-stage deals has been picked, necessitating a search for earlier candidates.

Additionally, drug companies are becoming wary about making the big upfront payments associated with recent late-stage deals and shouldering as much risk as they have been. Compare the Pfizer/Neurocrine Biosciences deal of 2002 with last December's AstraZeneca/AtheroGenics deal[2]. It has been reported that Pfizer paid San Diego-based Neurocrine $100 million upfront for the insomnia compound indiplon, agreed to pay up to $300 million in milestones and royalties estimated at 26–30%, and committed to fund the remaining product development costs. Whereas Pfizer was burdened with the remaining risk, in the AstraZeneca deal, involving a novel VCAM-I inhibitor in phase 2 clinical trials for atherosclerosis, AtheroGenics, in Alpharetta, Georgia, is responsible for funding the phase 3 clinical trial. AstraZeneca also paid less upfront ($50 million) and shifted payments downstream, with $300 million in development milestones, $650 million in sales-performance milestones and royalties estimated at 15–35%.

Although the numbers may be tempting for biotech companies, we have heard venture capitalists (VCs) express caution about striking a deal with big pharma too early in the product development process. One VC stated unequivocally that he believes it is misguided to view a corporate collaboration as a safe alternative to a dilutive, preferred-stock financing. If the biotech is not careful about the rights it gives away and those it retains, its loss of future growth potential to the pharma partner will strip far more long-term value away from the company's founders and investors than would an equity financing (see Box 1 and Box 2).

The marriage of biotech and medtech

It is becoming more commonplace to see deals involving both biotech and medical device technology, as entrepreneurs market new products that take advantage of the therapeutic benefits of a drug and the mechanical features of a device as, for example, device-based drug therapy such as insulin pumps, therapeutically active devices such as drug-eluting stents, and other products such as orthobiologics, artificial skin or tissue-engineered products[3]. For a deal to be successful, the medical device and biopharmaceutical partners have to understand each other's differences (in areas such as the regulatory approval process) and bridge the gap between engineers and biologists.

Perhaps buoyed by the success of Boston Scientific's Taxus, a paclitaxel-eluting coronary stent, more companies are seeing convergence as part of their future. For example, Cambridge, Massachusetts-based Genzyme and Minneapolis, Minnesota-based Medtronics have formed a joint venture, MG Biotherapeutics, to collaborate on cell therapy approaches to repair damaged heart tissue, and Genzyme and Lincoln, Rhode Island-based RenaMed Biologics have agreed to jointly develop and commercialize RenaMed's novel bioreplacement therapy to treat acute renal failure.

Cost and profit-sharing arrangements and copromotion rights

Until fairly recently, a partnering arrangement invariably involved the payment of royalties on net sales by the pharma company commercializing the product to the biotech company licensing the product. Such a deal structure also included other forms of payment, such as upfront fees, milestone payments and perhaps equity, and usually one party funded the development work on the product. Recently, however, cost and profit-sharing arrangements, where the parties share the costs of developing and marketing the product, including development, regulatory approval, manufacturing and marketing expenses, are increasing in popularity. The parties then share profits consistent with the percentage of each party's cost contribution.

Cost and profit-sharing transactions have clear advantages over royalty-based deals. The licensor company receives a much greater share in the upside if the product is successfully developed. For example, a payment of a 10% royalty on net sales of $1 billion would be $100 million, whereas a 50% share of profits on those sales may be two or more times that amount. Another benefit for the biotech partner is a larger role in decision-making during the development phase. Shared costs also bring a greater incentive to keep those costs down.

On the other hand, cost and profit-sharing transactions come with potential disadvantages as well. First, they require a higher level of funding during the development phase, often at a time when an emerging or mid-sized company may have limited resources. If the smaller company cannot keep up with its share of development costs, which may rise in unforeseen ways as development proceeds, then its share of profits typically proportionately decreases or the agreement may be converted to a royalty deal. Also, if a profit-sharing arrangement is used, one party may push to have the parties also share potential downstream liabilities (such as product liability claims) and the costs of insurance. Finally, these types of agreements tend to be more complex to negotiate and administer because they entail more accounting and reporting.

There seems to be an overall trend, particularly under a profit-sharing arrangement, for the smaller party to get a copromotion right, where each party uses its sales force to market a single brand, often in specified geographic territories. Copromotion is increasingly used by companies as a means of getting a sales force up and running, which is critical as they transition from discovery companies to fully integrated ones. Less frequently, a party may get a comarketing right that differs from a copromotion right in that each party independently markets the product under its own label, so that the two independent sales forces are essentially competing with one another.

Private versus public markets

In 2005, the number, size and valuations of initial public offerings (IPO) by life science companies, as well as the aftermarket performance of recent public market entrants, continued to be disappointing. For example, from 2003–2005, the average annual step-up in IPO valuations of biotechs—calculated by dividing the valuation investors receive when their company goes public or is acquired by the amount they invested in the company in private rounds of financing—hovered at or below 2x, compared to almost 4x during the period of 1999–2000 (ref. 4). Additionally, whereas the 26 venture-backed life science IPOs accounted for close to half of all venture-backed IPOs in 2005, they accounted for only three of the ten best-performing and seven of the ten worst-performing venture-backed IPOs[5].

At the same time, both fund-raising by life science–dedicated venture capital firms and their investments in biotech and medical device portfolio companies remained strong. Life science VCs raised close to $6 billion from limited partners, an increase over 2004 (ref. 6), while private biotech companies raised close to $3.8 billion[7] and medtech companies in excess of $2 billion[8]. The continued optimism reflected in early and mid-stage biotech investing may in part be due to the continued strength in the M&A markets during 2004 and 2005, where a sampling of ten acquisitions showed an average step-up from private rounds of about 4.94?, with an average sales price of between $200 million and $250 million compared to an average amount raised in private financings of about $55 million per company[9].

More money in fewer deals

Although VCs continued to invest greater amounts in life science companies in 2005, they made larger individual investments in fewer companies, with three of the largest ever Series A financings occurring last year[10]. San Diego startup Verus Pharmaceuticals raised $98 million in June, followed in size by the $70-million Series A round of Cerimon Pharmaceuticals based in S. San Francisco, California, in October. And the trend towards larger biotech venture capital financings is not limited to early-stage companies. The average size of Series A rounds in 2005 was $21.3 million, the average size of Series B rounds was $23.9 million, the average size of Series C rounds was $26.3 million and the average size of later rounds was $39.9 million[11]. Xanodyne Pharmaceuticals of Florence, Kentucky, for example, raised $170 million in a late-stage round.

This trend is not surprising, given that the average time period between a biotech company's initial funding and IPO has grown from four years to six over the past several years[12]. Investors we have spoken with emphasized that VCs must now fund biotech companies through major proof-of-principle events because the public markets are generally no longer willing to fund preclinical or early clinical development. Others blame the slowdown in the IPO market on the higher expenses of being a public company resulting from Sarbanes-Oxley compliance[13]. Regardless of the reason, the result is that venture capital investors now insist on financings that are large enough to bridge the portfolio company to the achievement of very specific milestones that will position it for either a subsequent financing at an increased valuation, a corporate partnering transaction or a sale.

Milestone-based tranched financings

With the growing size of their early-stage financings, investors are taking measures to ensure that their portfolio companies stay focused on putting the money to the right use. For example, most of the Series A financings of life science companies that our firm worked on in 2005 entailed so-called tranched financings, in which only some portion of the total committed capital is invested at the first closing. The investors' obligation to fund the full amount of the financing remains contingent on the company's achievement of certain development milestones.

Although staged financings are certainly not new, we are seeing them more often and with certain recurring features. For example, they are now invariably based on milestones, whereas in the past they were frequently based on burn rate or even the passage of time. Additionally, the investors get the benefit of a flat per-share price in the subsequent rounds, rather than a step-up in valuation. The goal, according to one VC, is to avoid the inevitable pitfalls of having "too much time, too much money" that otherwise result from large financings. This same VC explained that his firm always retains the right to invest the full amount at any time up to a certain future date, whether or not the milestones are met, in part because the milestones do not always end up reflecting the most relevant goals for the company's development. In fact, a risk of milestone-based closings is they may ultimately prove to be misguided and hence distract the scientific founders from more productive goals.

Venture capital investors also appear to be investing more effort in ensuring that the clinical development program described in a potential portfolio company's business plan makes sense and is realistic. Because setting the wrong goals in the program or getting the timing wrong by just a little bit can have disastrous consequences in subsequent fund-raisings, VCs are engaging medical consultants as clinical advisory panels to validate and modify the programs as a prelude to making their investments. The panels are asked to determine, among other things, whether the investors are funding to the appropriate endpoints based on the correct assumptions.

Extreme sensitivity to valuation

The VCs we surveyed emphasized their sensitivity to not overvaluing their potential portfolio companies. Given the weakness in the public markets and caution at the US Food and Drug Administration (FDA), which result in the need to fund more expensive and time-consuming product development cycles with private money, VCs remain conservative in the pre-money valuations of the companies they are funding. One VC observed a disconnect between the valuations legacy investors ascribe to their portfolio companies and the valuations at which potential new investors are willing to fund. He sees this phenomenon as a holdover of the inflated valuations of startup companies in the years 1999–2001, and the misguided inclination to value one's investments based on the amount of money invested rather than future prospects.

Who is getting financed?

Finally, the biotech companies that received the venture capital financing in 2005 and into this year continue to be those developing therapeutic compounds, especially in the areas of oncology and central nervous system disorders. Companies such as Cerimon that focus on in-licensing later-stage drug candidates accounted for 11% of life science venture capital financing[7]. In light of the reticence by the FDA to approve new chemical entities unless their perceived medical importance significantly outweighs any toxicity issues, venture capital investors are focusing on compounds that are either unlikely to face competition or have proven to be well tolerated.

One VC we spoke to maintains that investors are still shying away from pure technology companies such as Cambridge, Massachusetts-based Alnylam, which he considers somewhat of an aberration. Although his venture capital firm does invest in discovery companies, it only does so where the company's platform has generated promising drug candidates and its business plan is exciting. Indeed, platform companies increasingly appear to be screening known compounds that are in later stages of development or have received regulatory approval for other indications. Given the increased interest by big pharma in early-stage compounds and drug discovery platforms, some predict that VC interest will soon swing back to discovery companies as well[14].

Although convergent technology licensing deals between biotech and device companies increased in 2005, the amount of money being invested in convergent startup companies remained quite small. So far, investors continue to see convergent companies as particularly risky, potentially combining the long and uncertain product development life of biotechs with the smaller returns on investments of device companies[3].

Box 1: Licensing myths debunked

1. **It's important to do the first big deal, even if the terms aren't optimal.** Although very valuable as public validation of the start-up's technology, too often start-ups, lacking leverage in the negotiations, end up agreeing to deal terms that haunt the company in subsequent deals.
2. **All licenses should be exclusive.** While exclusive rights are generally preferable in order to exclude competitors in the marketplace, companies should consider whether non-exclusive rights for certain technologies would be adequate. Non-exclusive deals are less costly.
3. **Don't worry about termination provisions.** Unfortunately, many partnering arrangements don't succeed for any number of reasons (scientific, change of corporate priorities, even breach), so it is important that the agreement clearly spell out the rights of the parties in the event the deal ends.
4. **Licensors can collect royalties on product sales for indefinite periods.** In the US, certain payments on product sales, if incurred after the expiration of the patent covering the product, may constitute patent misuse, thereby rendering the patent and license agreement unenforceable.
5. **A company can treat jointly owned IP from a partnership the same as its solely owned IP.** In the US, joint owners of patent rights may each exploit and license without consent or accounting to each other; however, this is not the case in many countries outside the US.
6. **A small company has to partner in order to obtain funding for product clinical trials.** In addition to venture financings, other creative project financing vehicles exist that allow the startup to retain control over the product. For example, companies such as Clinical Development Capital providing funding in exchange for milestone and royalty payments.

Box 2: Financing myths debunked

1. **IPOs are exit strategies for life science venture capitalists.** IPOs are financing events for life science companies. VCs are often required to invest alongside the institutional investors to support the IPO and choose to continue to serve on the company's board of directors for years after the IPO to monitor their continuing investment.
2. **Life science companies can go public only during 'IPO windows.'** In the biotech IPO market, the focus is on the quality of the issuer, not on general market conditions. Windows will never open for weak companies, and will not slam shut for strong companies.
3. **Corporate partnering deals are nondilutive financings if they do not entail the issuance of equity.** Some biotech companies are doing licensing deals sooner than they should and are giving up too much of their potential upside in product development and commercialization. Unless a biotech can retain significant rights to its platform technology and drug candidates, it risks giving away too much value to its partner.
4. **Convergent startups combine the upside of biotech companies with the shorter product development cycle of medical device companies.** Although this may ultimately prove true, VCs are still very cautions about investments in true convergent startups, which accounted for only 6% of life science venture capital investments in 2005.
5. **'Series A Preferred,' 'Series B Preferred' and 'Series C Preferred' financings equate to the first, second and third rounds of financing of venture-backed biotech companies.** Names can be misleading, and optics can be everything. Especially in down-round financings, later-round investors are insisting that earlier rounds be reclassified so that their investment appears to be early-stage rather than mid- or late-stage. For example, rather than invest in a Series D Preferred round, a VC may require that the existing Series A Preferred, Series B Preferred and Series C Preferred be reclassified as Series A-1, Series A-2 and Series A-3, respectively, so that they can purchase a Series B Preferred and appear to be participating in the second round of financing.

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