

Christopher Sweeney and Ned Israelsen of Knobbe Martens Olson & Bear argue that, when it comes to big pharma's research and development pipeline, the low-hanging fruit has been picked and it's time to tend the orchard

New opportunities beckon for big pharma

In recent years, big pharma's research drug development pipeline has been emptying more rapidly than it is being filled. Big pharma is looking more and more to small biotechnology companies to make up the deficit, with particular emphasis on late-stage opportunities. However, there is not enough of that low hanging fruit to meet the demand for new drugs. As a consequence, big pharma is recognizing that more aggressive efforts are necessary to fill the pipeline.

One part of the answer is to encourage early-stage discovery and development in small biotech companies. Most observers recognize that small, entrepreneurial start-ups are disproportionately innovative and agile in identifying and developing hits and leads. However, traditional venture capital sources have backed away from early stage discovery companies in favour of later stage investments. This is due in large part to the long development cycle for pharmaceuticals, the high capital requirements, and the large percentage of drugs that drop out of the pipeline. This leaves many innovative technologies with no commercialization pathway. Thus, ironically, while the pipeline is running dry, new technologies are dying on the vine for lack of support.

Big pharma is working to fill this funding gap. One of the most difficult critical issues in this process is how to handle the associated intellectual property.

The pipeline problem

Total spending on pharmaceutical research has never been greater. However, the number of new drugs launched has dropped significantly. According to the 2004 Industry Profile by Pharmaceutical Research and Manufacturers of America (PhRMA), pharmaceutical companies spent an all-time-high \$33 billion on research and development in 2003, more than double what was spent just eight years earlier. In contrast, only 30 new active substances (NASs) were launched in 2003, according to the New Product Focus Annual Review by Intercontinental Marketing Services (IMS), down from 36 in 2002. This represents an all-time low since IMS started monitoring NASs in the early 1970s and a 43% decline since 1997.

Despite these figures, innovation in the biological sciences is very much alive. In addition to private dollars, public spending on medical research has surged, with the US

NIH budget doubling over the past five years. The pipeline problem resides not in a shortage of scientific breakthroughs, but in a lack of funding to move them through the early and middle stages of development.

Many large pharmaceutical companies in-license late-stage products from smaller biotech companies, assuming responsibility for the expensive Phase III clinical trials. Although a number of such drugs still fail, that risk is much lower than it is for earlier stage opportunities. However, there are not nearly enough of these late stage opportunities to replace existing drugs going off patent. The reality is beginning to settle in that the low-hanging fruit has been picked, and increased internal funding by big pharma is not sufficiently filling the pipeline.

The supply side

The dot-com bust has sent capital providers scurrying for safety. Today's venture capitalists are much more likely to fund advanced development programmes that can be served up to big pharma in the near term than they are to fund discovery

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stage research. Most investors want an exit in five years or less, but the timeline for launching drugs now in discovery can exceed 10 years. As a consequence, the flow of venture money into discovery stage biotech has slowed to a trickle.

Rewards of early involvement

Big pharma has a vested interest in filling this funding gap. Beyond the general goal of reinvigorating the pipeline, early-stage involvement with discovery companies can provide unique rewards for large pharmaceutical companies. Collaboration with a small biotech company can provide access to its technology, allow input into research strategy, and ultimately, give rights in the resulting intellectual property. Early-stage collaboration also provides an opportunity for companies to expend a comparatively small amount of money now for enhanced access to drugs in the future. Also, given the high dropout rate of drug candidates, most pharmaceutical companies want to diversify their biotech investments.

One benefit of early-stage collaboration that is sometimes overlooked is the relationship forged between the parties. Successful collaborations are likely to lead to ongoing relationships. This, in turn, can provide enhanced access to future innovations. Beyond the formalities of licences and contracts, the familiarity between the parties can lead to valuable connections and opportunities. The people behind a technology are usually just as important as the technology itself, so building good relationships with creative people can bear fruit in many ways.

The relationships and insights flowing from a collaboration can also prove invaluable if the smaller company becomes an acquisition target. The resulting familiarity with the people and the technology can greatly reduce the risks of an acquisition and reduce the diligence usually associated with such transactions.

Handling the intellectual property

In collaborations between early stage biotech and big pharma, intellectual property is a critical issue. The temptation for any investor is to maximize input into the funded research and secure access to the resulting intellectual property. With discovery-stage companies, however, such access could be counter-productive in the long term. First of all, the amounts of money invested by the big pharma partner will be a small fraction of the cost of acquiring a late-stage project. Thus, it is reasonable that ownership and control of IP should be correspondingly reduced. Second, a major strength of discovery-stage companies resides in their autonomy. Too often, big pharma's participation brings with it bureaucracy and control that can stifle innovation. Finally, big pharma must be careful to preserve the potential rewards that motivate entrepreneurs. Multiple rounds of investment are usually necessary to bring a drug product to the market. Pledging its IP or products to one partner at an early stage would probably make a small biotech company unfinanceable. If rights to a small company's major products are already locked up, venture capitalists will usually stay away. At the same time, collaboration with big pharma provides credibility that may facilitate outside investment.

Deal structure

Although the parameters of the agreement will often be unique to each collaboration, certain broad principles are usually applicable. In addition to satisfying their cash flow requirements, small biotech companies must also retain their identity and vision. The primary objective of big pharma should be to fill the early pipeline. Capital is required to nurture early discovery and create future opportunities. Future deals may lead to more control and ownership, but in early collaborations, it is best not to attach too many strings. Creative deal structur-

ing is necessary to meet each party's needs while minimizing the impact on the smaller company's IP.

Equity investment

Perhaps the most innocuous form of collaboration from an IP perspective is equity investment. Some pharmaceutical companies have affiliated with or actually established venture capital funds, such as SR One (GlaxoSmithKline PLC) and the Novartis Venture Fund (Novartis AG). Alternatively, the pharmaceutical company could make a direct equity investment in its biotech partner. In making such investments, however, big pharma runs into the same problem faced by the venture capitalists: discovery stage companies often do not pencil out from a pure equity perspective. With long development cycles and future cash needs, an appropriately low valuation can demoralize the entrepreneur and cause control issues, while a higher valuation leads to the risk of a down-round in the future. In such cases, it is often better to structure the equity investment as only one piece of a larger collaboration.

Sponsored research

Sponsored research agreements are widely used in collaborations between commercial companies and academia. Many universities, such as the University of California, require that the research support be treated as a gift. Often there is only an unwritten understanding that the parties will negotiate with each other for future IP rights. More typically, product rights are the subject of a right of first negotiation or an option. Such agreements can also be used in big pharma/small biotech collaborations. By eliminating or delaying any encumbrances on the intellectual property, such arrangements provide the breathing room that small biotech companies need.

No-strings testing

Many large pharmaceutical companies are entering into small scale no-strings-attached collaborations. These can involve, for example, running coded candidate compounds through big pharma's internal assays, engaging the small partner to perform contract research, or funding proof-of-principle development of a specified subset of a broader technology. Such collaboration, while not tying up the intellectual property, nevertheless provides value to each party. The larger partner develops a better basis for evaluating the opportunity, while the smaller partner gets research support. In addition to feeding the pipeline, such collaborations lay the groundwork for future collaboration.

Limited scope collaboration

Where a technology has potential applicability in a number of fields, big pharma may more appropriately obtain product rights limited to one specific product area. Such collaboration allows big pharma to protect the value of its investment through defined future product rights. The smaller partner gets research support, proof of principle, and credibility from the collaboration, while retaining all other product areas to bolster company value. Such agreements usually contain licensing provisions that allow each party necessary access to technology of more general applicability that arises from the collaboration.

Regardless of whether the deal structure involves sponsored research, grants, equity investments, active collaboration, rights of first negotiation, options, or field-limited licences, the bottom line is that big pharma must step up outside investment in the innovative process. By creatively structuring deals that do not overly encumber the resulting intellectual property, such collaborations can fill the research pipeline and provide badly needed support for discovery-stage research.