

# FLEXION EXPLOITS BIG PHARMA As Discovery Supplier

*Turning the tables on biotech, Flexion tries to finance and profit from Big Pharma's development logjam. It's one of several new attempts to do so.*

**ROGER LONGMAN**

- Big Pharma, unable to exploit its own research productivity, is increasingly seeing itself as a supplier of discovery assets.
- That's bad news for discovery-based biotech, but good news for companies with a talent for faster, more predictable development capabilities.
- Flexion, built around Lilly's fast-to-proof-of-concept strategy, is attempting to take advantage of the trend; it's in-licensed five products from three Big Pharmas.
- CROs and private equity investors are building alternative models to Flexion.

Since its formation in the fall of 2007, **Flexion Therapeutics Inc.** has apparently had no trouble getting Big Pharmas to let them review their shelved compounds, 130 or so of them from eight to 10 companies.

The start-up's basic message—cheap and rapid proof-of-concept of untested compounds—resonates with large drug companies. (See "Flexion: The In-Licensing Advantage of Cheap Proof-of-Concept," *START-UP*, December 2007.) And for good reason: Big Pharma's discovery productivity has far outstripped their development capabilities. Meanwhile, the size of coming generic losses and the inadequacies of their late-stage pipelines have increased their desperation for new products—but limited their abilities to pay for them. Companies have cut way back on the therapeutic areas they're willing to explore, leaving dozens of early-stage compounds stranded within their organizations.

That's why they're exploring how best to develop, externally, with other people's money, the de-prioritized fruits of their discovery groups. **GlaxoSmithKline PLC**, **Roche**, **Pfizer Inc.**, **Eli Lilly & Co.**, and **Merck & Co. Inc.** have all signed variations of deals in which they send the fruits of their

discovery groups to other companies, or even academics, for further development, sometimes with strings attached, sometimes without.

**AstraZeneca PLC** is perhaps the most radical of the new out-licensors. It's decided to get out of areas it once spent lots of money on (like lower GI medicines, disease-modifying arthritis therapies, and various CNS indications) and not enter areas in which it had early discovery efforts. Thus it's sent early-stage compounds to **Nestle SA's Alcon Inc.** (any potential ophthalmology medicines), **PsychoGenics Inc.**, **Celleron Therapeutics Ltd.**, and **Albireo Pharmaceutical** (a start-up formed around a set of AZ's gastro-intestinal compounds). It signed up with Merck so the two companies can test each other's early-stage cancer compounds in combination therapy. And it also liked Flexion's message, in June licensing the start-up an early-stage molecule.

AZ was Flexion's third partner. Together with three molecules from a still unnamed partner it signed up in January 2009 and one from **Merck Serono SA**, the pharmaceutical unit of **Merck KGAA**, Flexion now has a portfolio of four compounds (after further study, it has given back one of the

compounds it got from the unnamed partner), all more or less following an anti-inflammatory theme (ulcerative colitis, osteoarthritis and another two undisclosed indications). And while it continues to look for more in-licensing candidates, its current portfolio was apparently large and attractive enough to seal the deal for Flexion's Series A financing—convincing Sofinnova Partners to join Versant and 5AM Ventures to fill out the \$33 million round.

Like virtually all other first-round VC investments, Flexion's was hard to pull off. It took the company more than a year and a half to secure a third investor and thus enough money to get to what CEO Mike Clayman, MD, says are "value-inflection points for a significant portion of the portfolio." VCs were looking for "reasons not to do deals," says Clayman—echoing the challenges dozens of other start-up CEOs are facing.

But ultimately Flexion managed to convince its new investor that it was tapping into one of the most significant movements in the pharmaceutical industry: the strategic recognition that drug companies must learn to exploit far more of the research opportunities they both create and uncover but cannot afford to pursue on their own. As much as pharma is currently a discovery consumer, it must also learn to become "a discovery supplier," says Jan Lundberg, MD, until recently AZ's EVP, discovery research. "We're sitting on quality compounds but don't have the resources to develop them." AZ's Alcon arrangement, for example, includes molecules with mechanisms intended for non-ophthalmic indications but which couldn't be made sys-

temically available for one reason or another. "We thought about developing an ophthalmic capability," says Lundberg, recently appointed to run R&D at Eli Lilly & Co., "but decided that other people already had the skills—and the financing. We figured [that a deal with Alcon] would be a way we could participate in a broader field" without incurring the same economic risk.

The more AZ and its competitors send molecules outside for development, the more it turns the basic model of biotech—sellers of discovery to pharma—on its head. Biotech and their investors are instead becoming pharma's development financiers. That's bad news for discovery-based biotech: their wares, competing with those from Big Pharmas, will continue to fetch poor prices. But good news for companies with a talent for faster, more predictable development: they'll be buying assets at cheaper prices and thus building in a lot more margin for profit.

**BOTH COMPOUNDS AND PHILOSOPHY ROOTED IN BIG PHARMA**

Flexion's intellectual and managerial roots lie in Lilly's experimental development group Chorus. (See "Lilly's Chorus Experiment," IN VIVO, May 2007.) Its basic principle: since any early-stage compound is far more likely to fail than succeed, it should only do those experiments that show whether the compound works in people. Chorus thus eschews traditional pre-POC tasks, like heavy-duty CMC and formulation work that are predicated on the assumption that the product will work. Chorus founder Neil Bodick, MD, calls Chorus' behavior "truth-seeking" as opposed to the "success-based" attitude prevalent in drug development. Moreover, Chorus works with a very small footprint—most of the clinical development is outsourced.

And from what we can tell, Chorus is working. According to Lilly's Rob Arm-

Exhibit 1

**Selected Big Pharma Out-Licensing Deals in 2009**

OUT-LICENSING PHARMA/IN-LICENSER	TRANSACTION
AstraZeneca/Alcon	Exclusive ophthalmic rights to set of preclinical compounds
AZ/Celleron	Exclusive worldwide rights to preclinical HDAC inhibitor
AZ/PsychoGenics	Rights to evaluate AZ's compounds for potential in CNS diseases
AZ/Merck	Combination study of each other's Phase I-II oncology compounds
Lilly/Adolor	Exclusive worldwide rights to Ph I OBD candidate
Lilly/Implicit	Exclusive worldwide rights to Phase II antibody for acute lung injury
Pfizer/The Medicines Co.	Global rights to naturally occurring protein APO-A1 for coronary artery disease
Pfizer/GSK	JV combining HIV businesses—Pfizer's biggest contribution is its pipeline
Roche/Afferent	Exclusive worldwide rights to Ph I chronic pain program

SOURCE: Elsevier's *Strategic Transactions*

strong, PhD, who as VP, global external R&D, is in charge of the effort, the company has put 28 NMEs into the system—it started with 11 five years ago. It's completed 14 proof-of-concept studies. Five were positive and four of those are now in Lilly's main development group (the fifth is being out-licensed). Armstrong expects to see the first NME to have graduated through Chorus launched before 2014. (See "Lilly Tries to Buy Time," IN VIVO, December 2009.)

Chorus has been successful enough, says Armstrong, that the company joint-ventured with India-based **Jubilant Organosys Ltd.** to combine Chorus' rapid-POC model with Jubilant's lower cost structure. And now it's setting up a Chorus clone in Indianapolis (the groups have to stay small to be effective—roughly 30 people can handle 15 molecules, he says; but any bigger and the group loses focus and speed).

But although Chorus is now moving in that direction, it has not yet fully taken its show on the road—that is, using Chorus to attract in external assets or develop internal assets with external financing.

Which has left Flexion with an opportunity. The start-up offered companies a deal: license it a market-basket of early-stage de-prioritized compounds. Flexion would fund the proof-of-concept work. If one or two looked particularly appetizing, the pharma could buy them back for an up-front fee, milestones and royalties. The others would stay with Flexion as part of its proprietary pipeline—and on which, if they succeeded, Flexion would pay milestones and royalties. In both cases, the licensors would get someone else to pay for at least early development (and thus the data required to make a decision about full-scale development) and at least some value from a molecule that would otherwise have never seen the light of commercial day.

### MARKET-BASKET IN-LICENSING: THEORY AND REALITY

It was a good theory—and it more or less worked. In January 2009, the unnamed partner licensed three compounds to Flexion, following Flexion's original market-basket concept. But the idea was a little too aggressive for the other licensees. Merck Serono and AZ each licensed Flexion a single com-

pound. In one case (Clayman wouldn't say which), Flexion will own the molecule outright. In the other, the licensor has a chance to get it back, albeit in a complicated fashion and one that gives Flexion a co-development option and thus a bigger share of the end proceeds. Both of those deals, however, envision the possibility of adding more molecules to the package: they want to see how Flexion handles the first one before they expand the deal (apparently, however, both AZ and Merck Serono are already discussing other molecules with Flexion).

It also took longer than expected for Flexion to find and sign up for the molecules it needed, in part because it was in fact doing things differently than Clayman and Bodick had done them at Chorus. In the first place, they needed to do more due diligence. Lilly had already done enough research, before putting a molecule into Chorus, to know whether the molecule had the potential to be first- or best-in-class. But in looking over in-licensing candidates at Flexion, "we needed to convince ourselves," says Clayman.

Moreover, once past the quality hurdle, Flexion couldn't simply take all comers. Its business model posited out-licensing molecules once they'd shown some convincing proof of efficacy—but there was no guarantee it could find such a partner. And if it couldn't, it would have to put the molecules through pivotal trials on its own, which meant they had to work for indications Flexion could afford to pursue. "We needed molecules," says Mike Clayman, "that would attract a large pharma with POC data—but which would also lend themselves to an emerging spec pharma company so we could do it ourselves if need be."

### BIG PHARMA OPPORTUNITIES, SPEC PHARMA ECONOMICS

The criteria, in short: near-term end points; minimal chance for molecule-derailing side-effects; big unmet need; focused marketing requirement. For example, Flexion is working on an osteoarthritis drug with disease-modifying potential. But the trials required to prove such a benefit (demonstrating the correlation between an improving morphology and a clinically relevant improvement in symptoms or outcomes) would probably take more than two years—and most, if

not all, Flexion's cash. But the compound does have potential as a pain medicine and since it's delivered as an intra-articular injection, won't have systemic effects. The current market, roughly \$500 million according to Clayman, is dominated by intra-articular injections of hyaluronic acid and steroids. "It's an established market, ripe for innovation," says Clayman. And besides, these drugs are mostly delivered by orthopedists and rheumatologists, he notes, so Flexion—in case it has to take the drug all the way to market—won't need a GP sales force.

Another molecule in the Flexion portfolio is a reformulation of a marketed, still-patented product but for a new indication coincidentally modulated by the same mechanism. The condition is treated—poorly—by a different medical specialist. The Flexion drug has few side effects—and a reasonably sized investigator-sponsored trial in the new indication showed big improvements.

Flexion's model—highly predictive development programs, big market opportunities, spec pharma clinical and commercial economics—has certain inherent limitations. That's why it won't likely have many start-up competitors but also why CROs have picked up on the idea. They can leverage their cash flow and infrastructure to allow them to do a broader set of molecules. **Quintiles Transnational Corp.**, for example, recently signed up with **Eisai Co. Ltd.** to apply rapid proof-of-concept development to six of the Japanese company's oncology candidates it doesn't want to fund on its own. Quintiles will go at risk on the project—it will make most of its money on success-based milestone payments though presumably it will also be in the pole position to supply late-stage development services. "With Eisai, they do have oncology expertise and they just have more very important assets and trials to manage than they have capacity," says Ron Wooten, president of **NovaQuest**, the Quintiles unit responsible for the deal. So Quintiles acts as an extension to Eisai's oncology expertise, both in terms of trial design and management. And it supplies cash. "With the Eisai deal, it's a true skin in the game, cash investment," says Wooten.

In another variation on the theme, **Pharmaceutical Product Development**

Inc. is putting \$100 million into Celtic Therapeutics Holdings LP, a private equity group building a portfolio of in-licensed products it will then sell off to other drug companies. It will also be Celtic's preferred supplier of clinical development—so it will make money both on the equity side of the deal and as a service provider. PPD simultaneously spun off its own compound partnering business, along with another \$100 million. That program was philosophically similar to Flexion in that it takes early-stage compounds and, on its own nickel, develops them through proof-of-concept before out-licensing them. But that business hit PPD's expense line, depressing earnings. The new arrangements allows PPD to participate in the same out-licensing phenomenon of which Flexion is trying to take advantage, but by leveraging its balance sheet cash, not immediately exposing its P&L.

In both cases, the CROs can theoretically participate in the economics of a broader variety of molecules than can Flexion. In return, they give up the kind of control, and the level of upside, that Flexion's VC-supported model requires.

Meanwhile Lilly is trying to create Flexion-like economics in part by using Chorus as the nexus of both in- and out-licensing. Indeed, Chorus is central to Rob Armstrong's vision of disaggregating what he sees as the three components of R&D—funding, molecule-sourcing, and development capabilities. The group represents

a way of taking advantage not merely of Lilly's own oversupply of early-stage innovation but of the external oversupply as well, he says. The molecules in Chorus and its clones could represent a "mirror portfolio, a virtual external portfolio," that could be funded by Lilly or in part by outsiders, in effect, the role that Flexion is playing for its licensors.

Armstrong is hoping that one attraction Chorus will offer venture capitalists is a way to focus their funding on advancing molecules, not building corporate infrastructure. "Some VCs will be attracted to the idea of spending 80% of their money on progressing molecules and 20% on people and infrastructure. If a VC had managed to pull together 10 compounds, he'd probably have five companies built around them. Sometimes you need dedicated infrastructure. But sometimes you get a set of molecules which don't require that kind of overhead—but just the ability to prosecute proof-of-concept."

Armstrong's disaggregation strategy goes far beyond Chorus. "We'll need a suite of models, a variety of business networks, that allow many ways of creating value," he says. (See "Lilly and Merck Lead the Way With Asian FIPNet Strategies," *IN VIVO*, May 2008.)

But it's easy to miss the forest for the trees: Lilly, like Flexion, Celtic, PPD and Quintiles, are all looking to take advantage of a big change in the Big Pharma R&D model, in which a large percentage of their discovery assets are developed by

other companies, whether those companies are completely independent—like Flexion—or partly so, like Chorus. Says Jan Lundberg: "I believe that the majority of internal discovery will at least be intended for internal development. But external development is increasingly doable. And it's going to increase." AZ won't develop molecules that fall into core therapeutic areas outside the company, he says. Nor will it develop molecules outside the company for indications it's also developing molecules for inside. But AZ "needs more shots on goal, particularly with novel targets." And that means AZ, and other companies, will have to start thinking of their discovery groups in ways very similar to how biotechs have always thought of themselves—as discovery suppliers to the rest of the biopharmaceutical world.

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COMMENTS: Email the author: [R.Longman@Elsevier.com](mailto:R.Longman@Elsevier.com)

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