

BIOTECH R&D

Flexion: The In-Licensing Advantage of Cheap Proof-of-Concept

In 2002, **Eli Lilly & Co.** began to experiment with a radically new process for clinical development: rapid proof-of-concept (POC). It was by no means the first such experiment in the industry, but Lilly has been the only company to stick with it, institutionalizing the ideas in its quasi-independent Chorus division (See “Lilly’s Chorus Experiment,” *IN VIVO*, May 2007).

Now Chorus’ two top executives are going out on their own, setting up a Chorus-style competitor called **Flexion Therapeutics Inc.**

The basic and differentiating principle behind Chorus, and Flexion, is the assumption that any early-stage compound is far more likely to fail than succeed. Thus Chorus only does those experiments that show whether the compound works in people and thus allows a development organization to more confidently proceed with more expensive late-stage trials, or more confidently kill it (drugs are often shelved with relatively little evidence of their inadequacies). That means that Chorus eschews the other traditional pre-POC tasks—like heavy-duty CMC and formulation work or longer-term carcinogenicity testing—necessary for developing a successful candidate but which can be done later. Chorus founder Neil Bodick, MD, calls Chorus’ behavior “truth-seeking” as opposed to the “success-based” attitude prevalent in drug development.

The second principle behind Chorus is externality: the unit has just 22 employees—located outside of Lilly’s of-

fices—and they outsource to CROs and consultants most of the actual drug development work. The small group is all about communication and efficiency, not infrastructure. Nonetheless, this handful of people are now developing a significant portion of Lilly’s total early-stage compounds for roughly a third of the per-molecule cost while saving up to 18 months on the time to proof-of-concept. Con- tends the former general manager of the division, Michael D. Clayman, MD: Chorus is 8-10 times more productive than the rest of the industry in getting compounds through POC.

It’s that kind of productivity on which Clayman and Bodick, backed with an initial and unsyndicated \$3 million from Versant Ventures, want to capitalize with Flexion—using the Chorus model to build a product-focused business developing the shelved compounds Big Pharma hasn’t figured out how to exploit.

Lilly, too, had recognized the opportunity to leverage Chorus to cheaply expand its own in-licensing program and monetize the value of programs it doesn’t want to take forward. In January 2007, Lilly signed a deal with Versant to open up some of Chorus’ development capacity

to compounds the VC group uncovered through its EuroVentures in-licensing operation. Versant would fund Chorus’ development costs for Versant compounds, and would get some preferential access to Lilly compounds Lilly didn’t want to take forward. Meanwhile, Lilly would get some sort of access at POC to Versant molecules—sometimes a right of first negotiation, sometimes a right to license the compound at a predetermined price; a first look in any event.

But despite taking “a hard six-month run at the experiment,” says Versant partner Brad Bolzon, “it was too difficult to get the incentives aligned.” He wouldn’t go into specifics, but an observer can guess at a few of the problems. Versant compounds would compete with Lilly compounds for development time within Chorus—and generally Lilly compounds would win. Indeed, the more successful Chorus becomes within Lilly, the more Lilly molecules should flow into it, with less room for Versant’s candidates. Second, neither Versant nor Lilly would want its partner getting any sort of exclusive rights to their contributions to the Chorus pipeline—economically, it would be smarter to sell them to the highest bidder. And perhaps most importantly, the licensing sources of Versant’s compounds are often other drug companies—which would balk at allowing any Lilly division access to their IP.

It was that third problem that crys-

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tallized the opportunity for a venture-backed version of Chorus. In effect, Flexion will offer drug and biotech companies access to Chorus-style development, but without the overhang of a Big Pharma sponsor.

Flexion won't be a POC-focused services company. Instead, it will swap CRO-like development expertise in return for access to compounds. It is, in essence, an in-licensing company with a potentially compelling advantage over competing in-licensors. (See "The New Out-Licensing Start-Ups: Securing Product Supply," START-UP, December 2005.)

Says Clayman: "No one at Big Pharma skimps on Phase III or later trials. And discovery is pretty well funded, too. But everything in between is under significant pressure." That means there's little money for exploring otherwise interesting compounds that nonetheless fall out of Phase I or II trials, perhaps because they're seen as less interesting than others—often based on very little data—or because they're back-ups for candidates already in later stage. Indeed, the industry is full of examples of compounds that failed for an initial indication but which succeeded based on another—like raloxifene (*Evista*), originally for breast cancer but ultimately successful in osteoporosis, or, more famously, the hypertension-turned-erectile dysfunction drug sildenafil (*Viagra*)—or which were simply resurrected because the later-stage cupboard was bare, like **GlaxoSmithKline PLC's** lapatinib (*Tykerb*).

Because Flexion, like Chorus, can do this initial POC work with a lot less money and time than other companies, it can theoretically soak up a number of industry's orphan candidates. And because it's taking a lot less financial risk per molecule, Flexion should be able to afford to offer partners clawback rights to at least

some of their candidates. Clawbacks are often a big problem for in-licensing-based biotechs because they compromise returns: the more a biotech spends in development, the more it hurts to sell back a product to its original owner. That's why many in-licensing biotechs try to avoid clawbacks altogether—a big problem since without a right to repurchase the compound, many drug companies simply won't out-license it in the first place. But if Flexion can in-license multiple products and develop them to POC for comparatively small sums, it should be able to mix clawback options on some compounds with others for which it gets to keep rights.

Losing Clayman and Bodick is certainly a blow to Lilly's Chorus program, but hardly a fatal one, says Clayman's former boss Robert Armstrong, PhD, Lilly's VP, Global External Research and Development. There are plenty of internal candidates for the jobs.

More importantly, he says, Lilly no longer sees Chorus as an experiment, "which it was until early this year. It's now core to what we do." Though he wouldn't say whether any Chorus compounds have yet entered full late-stage development, he nonetheless believes the big questions about Chorus have been answered. The most important of those focus on the various shortcuts Chorus takes in order to get to an answer on POC: for successful

molecules, those tasks need to be done after POC, adding more time to the period before a Chorus can start late-stage development. But Lilly is now convinced that the savings on the front end more than make up for the extra time on the back end of the process—at least, says Armstrong, for those molecules for which biomarkers provide a clear POC signal.

In the last six months, Lilly has put more compounds into the Chorus portfolio. It's close to, and perhaps has reached, the maximum number of compounds Chorus can develop with its current staffing, and Armstrong says they're discussing whether to grow the group (which they probably won't) or clone it (which they probably will). The Chorus model works best, Armstrong and others believe, if it stays small.

Lilly is still toying with the idea of creating its own external Chorus. But its endorsement of Chorus is also an implicit endorsement of this new competitor. Flexion partners will feel better about experimenting with Lilly's idea, which in any event won't entail much financial or organizational risk.

Meanwhile, Flexion will face a different challenge: its model can't be patented. The more successful it is in finding partners, the more companies will try to copy it. That's why Flexion has to run as fast as it can toward capturing enough products to create a truly proprietary business.

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—ROGER LONGMAN

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