

Pharmaceutical Strategic Outlook: The Trouble with Alliances

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Summary: At Windhover's March 2008 Pharmaceutical Strategic Outlook meeting one overriding theme was an alliance paradox: values continue to rise and deals provide an increasingly important source of funds for biotechs, yet public investors don't seem to like these deals. Plus: a discussion of big-pharma outlicensing and the importance of CFOs in pharma strategy.

Further Analysis:	Title	Magazine	Issue	Article ID
	AZ Joins Spin-Out Set, Forms GI Play Albireo	<i>Start-Up</i>	Mar. 2008	<u>2008900060</u>
	Pharma's New Follow-On Strategy	<i>IN VIVO</i>	Feb. 2008	<u>2008800020</u>
	Biopharma VC Exits 2005-2007: Cheap IPOs, Expensive Acquisitions	<i>Start-Up</i>	Jan. 2008	<u>2008900020</u>
	Flexion: The In-Licensing Advantage of Cheap Proof-of-Concept	<i>Start-Up</i>	Dec. 2007	<u>2007900237</u>
	Alnylam Takes Platform Monetization to a Whole New and Non-Exclusive Level	<i>IN VIVO</i>	Jul. 2007	<u>2007800122</u>
	Lilly's Chorus Experiment	<i>IN VIVO</i>	May 2007	<u>2007800083</u>
	BMS Deals Diabetes Drugs, Solidifies Specialist Stance	<i>IN VIVO</i>	Feb. 2007	<u>2007800028</u>
	Pharmaceutical Strategic Alliances 2006: Forcing Externalization at Big Pharma	<i>IN VIVO</i>	Oct. 2006	<u>2006800166</u>

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Windhover's Biopharma Team

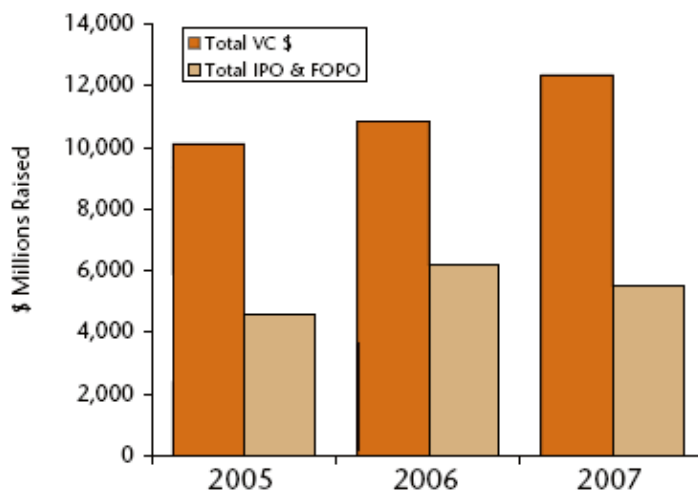
Among several topics explored at this year's Pharmaceutical Strategic Outlook and BIO-Windhover meetings was this troubling paradox: alliances, whose values continue to rise, are more important than ever to biotech's financial health, yet public investors don't seem to like these deals.

Biotechs have always relied on four sources of financing: venture capital, public equity, M&A, and alliances. When one or the other of these chair legs has weakened, biotechs have been able to lean on the others. But VC isn't enough. And public equity has virtually disappeared. Add up all the dollars invested in biotech IPOs and follow-ons over the last three years (\$16.2 billion) and it doesn't equal even half of what VCs and other private equity players have put into the industry (\$33.3 billion). (See *Exhibit 1*.)

Exhibit 1

Stingy Public Markets

SOURCE: Windhover's Strategic Transactions Database



There's certainly more M&A than there ever has been in biotech, but with about 11 private acquisitions of any significance per year, and a third the number of public acquisitions, investors can hardly count on such purchases to give them the minimal returns they require.

The only financing leg that remains strong is alliances. Average up-front payments—Windhover's favorite if oversimplified proxy for measuring the true value of an alliance—are increasing as well. (See *Exhibits 2 & 3*.) In other words, alliances are more important than ever to biotech.

Exhibit 2

Big Pharma/Big Biotech's Up-front Alliance Payments

SOURCE: Windhover's Strategic Transactions Database

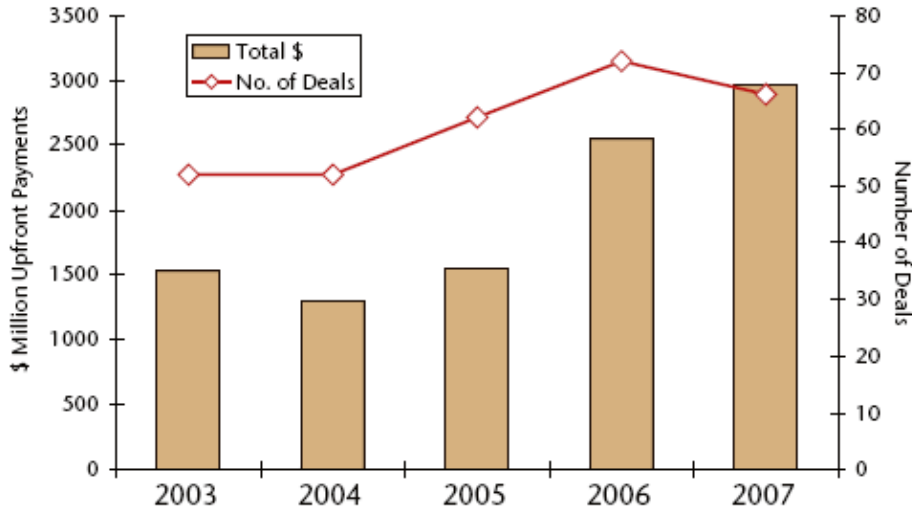
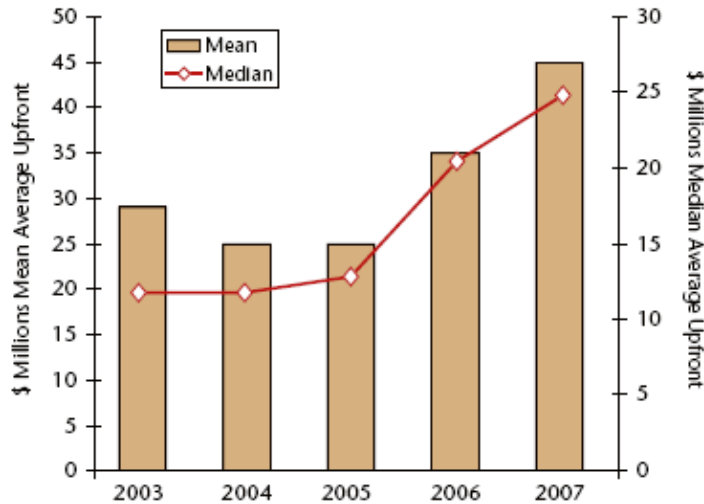


Exhibit 3

Average Up-front Alliance Values



SOURCE: Windhover's Strategic Transactions Database

When Licensing Bleeds Value

The problem is that alliances too often dilute overall corporate value.

For private biotechs being steered toward an exit by venture backers, alliances are only a net positive if they don't overcomplicate the buyout math and undermine what might be a lucrative acquisition later on. As long as acquirers are willing to pay a nearly 100% premium to what IPO investors are willing to pay, venture backers are unwilling to jeopardize a potential merger windfall by selling off rights to a key product. (See "Biopharma VC Exits 2005–2007: Cheap IPOs, Expensive Acquisitions," START-UP, January 2008 [A#2008900020].)

There are exceptions. A license can precipitate a takeout, for example, as in the cases of **Shire PLC's** deal—then—acquisition of **New River Pharmaceuticals Inc.** [W#200710027], and **Amgen Inc.'s** deal—then—acquisition of Abgenix (now known as **Amgen Fremont Inc.**) [W#200510208] The original deals struck by the acquirers amounted to "buying an option to be first in line" at the M&A table, pointed out Campbell Alliance's Ben Bonifant, at the opening plenary discussion for the BIO–Windhover meeting.

For platform technology companies the balance is slightly different, noted **Alnylam Pharmaceuticals Inc.** president and CEO John Maraganore, PhD, who suggested that Alnylam "would do more deals like the **Roche** transaction," which brought the biotech \$331 million in up–front fees and equity payments. [W#200720461] (*See "Alnylam Takes Platform Monetization to a Whole New and Nonexclusive Level," IN VIVO, July 2007 [A#2007800122].*) He added, however, that given concerns about the resultant dilution of the technology rights to Alnylam's RNA interference platform, this kind of broad, lucrative deal would only be replicable perhaps "a few more times." To reduce that risk, he said, in future deals Alnylam may choose to retain certain additional rights to resulting drug candidates.

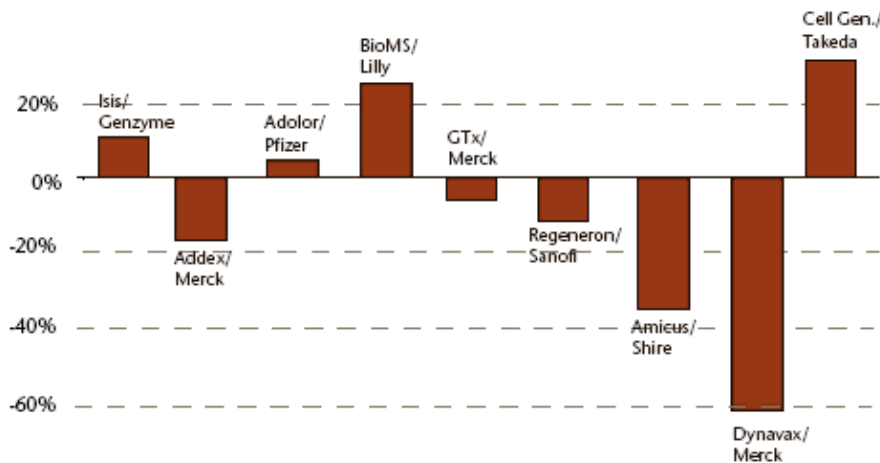
Whither Big Pharma Valuation?

Alnylam shares have certainly done well since its July 2007 Roche transaction (up about 60%). But its platform makes it exceptional. Since November 2007, there have been 9 deals by public biotech companies with up–front payments (equity and cash) of greater than \$20 million—a reasonable proxy for a large deal. Among them: **Isis Pharmaceuticals Inc.'s** mipomersen deal with **Genzyme Corp.** (\$325 million up front) [W#200820005]; **Merck & Co. Inc.'s** deal with **GTx Inc.** on its Phase II SARM and two backups (\$70 million up front) [W#200720768]; and **Sanofi–Aventis' multi–antibody arrangement with Regeneron Pharmaceuticals Inc.** (\$85 million up front). [W#200720829]

And yet, with all this supposedly undilutive capital flowing in, the market's reaction has been distinctly negative. Following the signing of a deal, the median share price among these nine biotechs is down 6%. (*See Exhibit 4.*)

Exhibit 4

Biotech Share Prices Since Deal Signing



SOURCE: Windhover's *Strategic Transactions Database*; Moneycentral.msn.com

The entire decline can't be blamed on the deals. For example, **Dynavax Technologies Corp.** signed a deal with Merck on its *Heplisav* hepatitis B vaccine, getting \$31.5 million in up–front monies. [W#200720758] As *IN VIVO* went to press, the stock had declined 66%—though that decline was almost entirely due to the fact that the company had to halt its *Heplisav* trial for safety reasons. And to be fair, equities in general have hardly been popular in the run–up to and aftermath of the Bear Stearns fiasco.

But you'd expect better from companies with good news. When Regeneron teamed up with Sanofi, it monetized its *VelocImmune* antibody production system for the third time. This time it added a rich co-development deal on a series of programs, with spectacular downstream economics. Nonetheless, the company has lost 12% of its value since it announced the deal.

The day the market heard of the Isis/Genzyme deal, Isis shares jumped 28%—undoubtedly helped by the amplifier of the JP Morgan conference, during which the deal was announced. (See "*Pharma's New Follow-On Strategy*," IN VIVO, February 2008 [A#2008800020].) Within a month, the company had given up most of those gains (pre-Bear Stearns debacle, mind you). It's now trading 11% above its pre-announcement price—despite what was certainly one of the biggest biotech deals in history and by far the largest in the long career of antisense technology.

There's a sort of dog-in-the-manger quality about all this. If investors won't put in new money, you'd figure they'd at least appreciate it when Big Pharma did. Certainly, they used to. At one time, a Big Pharma deal was the required validation for an IPO or additional public round. But now it's clear that the market no longer gives a damn about such imprimaturs. Big Pharmas' frequent missteps in development haven't shined up their product-picking reputations. More importantly, biotech's institutional investors now have the teams to do their own scientific and clinical homework.

An Issue of Control

In the end, investors just don't like some of the deals biotech is signing, despite the big dollars attached to them. One reason, noted Deerfield Partners' Bill Slattery at the BIO-Windhover meeting, is that deals often give Big Pharma development control.

The problem is that letting a biotech retain development rights isn't practical, argued Lisa Ricciardi (former licensing SVP at Pfizer Inc. and now an adjunct partner at VC Essex Woodlands) at BIO-Windhover. Drug companies would rather their biotech alliance partners stick to their knitting: research-based start-ups require different skill-sets than development-stage companies, which are again different beasts than commercial ones. "Most larger companies would argue that they have all the capabilities necessary to do development themselves, and they'd prefer a straight license," she said. Sharing development is only something pharma does if it absolutely has to, she added. The risk of coming up with contradictory or confusing data from different trials by different organizations is simply too great.

But Slattery and other investors are beginning to see things differently. Big Pharma frequently chases only the major indications for a biotech's programs, which may mean they ignore the smaller uses to which the molecule might be better suited—and for which it might be approvable. No approval—no milestones, no royalties, no value in the biotech, no brass-ring M&A shot.

Take Merck's deal with GTx. Merck paid the biotech \$70 million in cash and equity to get development and marketing rights to its Phase II SARM **Ostarine** (a terrific validation because **Johnson & Johnson** had given up rights to the same thing a few years before [W#200420211]), \$15 million in R&D fees, and a potential \$422 million in additional regulatory milestones.

But despite a 63% one-day jump—good data reported from its most advanced drug, the Phase III prostate cancer therapy toremifene (**Acapodene**)—the stock is still off from the day GTx signed its Merck deal. Indeed, over the three months following that deal, the company lost 33% of its value.

There were likely a variety of reasons for the decline. But one of them is that investors don't like the fact that Merck now has all development rights to **Ostarine**. Should toremifene fail, GTx's future will largely be in the hands of Merck. And for all Merck's good intentions, its first obligation will be to Merck shareholders. Which is why GTx shareholders have reason to be skeptical.

In short, even a lucrative co-commercialization right won't preserve a biotech's value if the development program is built to suit the Big Pharma's commercial ambitions, not the molecule itself.

Big Pharma Out-licensing and the Proof-of-Concept Model

You would have thought Big Pharma's increasing willingness to out-license would be good news for the industry. VCs love getting their hands on pre-baked assets; fully formed spinouts are even better—especially as these days, strings are a rarity.

But why are pharmaceutical companies out-licensing? Not out of the kindness of their hearts, certainly. And not because it's easy; getting GI-focused **Albireo Pharmaceutical** out of **AstraZeneca PLC**, the most recent example of the phenomenon, was a challenge that took months. [W#200830074] (*See "AZ Joins Spin-Out Set, Forms GI Play Albireo," START-UP, March 2008 [A#2008900060].*) They're doing it because cost-cutting and R&D prioritization demands it.

Plus, according to commentators at Windhover's **Pharmaceutical Strategic Outlook** conference in New York in March, Big Pharma's various R&D experiments (translational medicine, productivity metrics, and most recently, the in-licensing splurge) have led to a glut of Phase II programs. (*See "Pharmaceutical Strategic Alliances 2006: Forcing Externalization at Big Pharma," IN VIVO, October 2006 [A#2006800166].*) They can't afford to take all of them through expensive late-stage trials—which is why Jim Cornelius, **Bristol-Myers Squibb Co.** chairman and CEO, confirmed on stage at PSO: "There will be more [risk-sharing, late-stage] deals like that between BMS and AstraZeneca" in January 2007, referring to the pharma's 2007 deal with AZ in diabetes. [W#200720029] (*See "BMS Deals Diabetes Drugs, Solidifies Specialist Stance," IN VIVO, February 2007 [A#2007800028].*)

Even the prolific acquirer and infrastructure-rich **Pfizer Inc.** has started to (at least) talk about out-licensing—a subject that was previously taboo. "We have headcount for it," admitted Barbara Dalton, PhD, head of Pfizer's Strategic Investment Group, to the PSO audience. "There will be spin-outs in the future," she promised. Ellen Strahlman, MD, VP, worldwide business development at Pfizer, said on a later panel that even though Pfizer is "a little late to this party," its efforts would be successful in part because senior management has prioritized the plan, which commenced in August 2007. Whereas previous management was against spinning out assets and out-licensing, both Martin Mackay, PhD, Pfizer's R&D chief, and Jeff Kindler, chairman and CEO, are behind the efforts, noted Strahlman.

But if Big Pharma is going to want to shed some risk and responsibility on its development programs, what of the growing numbers of biotechs wanting to do much the same thing: bake assets as far as Phase II, or clinical proof-of-concept (POC), and then license them—for enough reward, in theory, to justify avoiding Phase III risk and cost?

They're driven—justifiably—by rising Phase II deal values, which are in fact increasing at a better clip than the values of those rarer beasts, Phase III deals. The question is how long that trend will last. So far, Big Pharma's woes have benefited biotechs, driving up deal financials, improving biotechs' leverage, and allowing them to hang on to more value.

But the point of the proof-of-concept model is that companies don't, for the most part, want to take on later-stage responsibility via co-promotion agreements. Now sure, the right Phase II programs will always be in demand, as Steven Lee, PhD, CEO of POC-focused **Summit PLC**, was quick to point out during a panel discussing the virtues of POC versus the fully integrated biotech model. And there's still virtue in this kind of low-risk strategy, he argued, particularly in Europe. **Flexion Therapeutics Inc.**'s COO Neil Bodick, MD, PhD, concurred: there's value in sticking to one's knitting; the "fully integrated model is going to de-construct," he predicted. For Bodick, "there are opportunities to be competitive in different [incomplete] segments of drug discovery and development." (*See "Flexion: The In-Licensing Advantage of Cheap Proof-of-Concept," START-UP, December 2007 [A#2007900237].*)

That's a neat argument, and probably a valid one in theory. (Commentators espousing the disaggregation of pharmaceutical firms feel it's particularly relevant to Big Pharma, even though the companies themselves don't seem to agree—see sidebar "*CFOs: Agents for Change?*".) In practice, though, the POC model has yet to prove itself. Even within **Eli Lilly & Co.**'s six-year-old Chorus experiment—the in-house inspiration for Flexion that likewise aims to get compounds to POC cheaper and faster than anyone else—"there's no data yet" on whether the model leads to a better downstream success rate (or simply nastier surprises for later), acknowledged Bodick. (See "*Lilly's Chorus Experiment*," IN VIVO, May 2007 [A#2007800083].)

Meantime, fully integrated biotech ("FIPCO") advocates such as **Rigel Pharmaceuticals Inc.**'s chairman and CEO Jim Gower or **NicOx SA**'s CEO Michele Garufi are still out in force, despite skyrocketing regulatory risk. How else has biotech ever created significant value, they asked from the stage at the PSO conference? The trend toward more specialist drugs, requiring small sales forces, makes going it alone plausible.

Sure, "you have to be a bit crazy" to undertake multi-thousand patient trials and build a sales force, acknowledged Gower. But with a broad portfolio, a handful of existing partnerships, and, most importantly, investors' green light to take a punt on the lead program, there's no reason to hand over the jewels. Especially if the value and number of Big Pharma deals do indeed lose their luster.

CFOs: Agents for Change?

Last year saw an unprecedented five new CFOs among the top drug firms—at **Pfizer Inc.** (Frank D'Amelio), **AstraZeneca PLC** (Simon Lowth), **Wyeth** (Greg Norden), **Amgen Inc.** (Robert Bradway), and **Merck & Co. Inc.** (Peter Kellogg). This re-shuffle led to the question, posed during a panel at Windhover's **Pharmaceutical Strategic Outlook** meeting in New York City, as to whether these money-men were going to be the drivers of (let's face it, necessary) change at Big Pharma.

Peter Kellogg joined Merck in June 2007, following stints in Big Biotech—at Biogen Idec—and in the consumer industry, at Pepsi, before that. What has he brought across from those sectors? The biotech experience allowed him to slip easily into the mega-dealmaking/collaborative culture that Merck has been touting for some years now, and the Pepsi learnings were useful in re-engineering cost structures (common in all Big Pharma these days).

Radically, Kellogg predicted more collaborations (especially risk- and cost-sharing ones) and more shrinking of SG&A. Will Merck shrink so much as to become virtual? "No, that would be too extreme," he said. But the share of overall R&D spend on internal infrastructure will decline in favor of external collaborations, and even then total spend will grow only in the mid-single digits. "We will bring in more from the outside, and we'll be smarter about where we run our trials, and where to find patients."

The other CFO-panelist, **Genzyme Corp.**'s Mike Wyzga, claims he's already applying lessons from his previous life in the software industry, where winning companies like Microsoft looked beyond the 10-year horizon to figure out how to grow. "From mid-07 we stopped giving quarterly guidance, and instead we predicted 20% in average compound earnings growth out to 2011," Wyzga explained. That, he argues, shifted the company's outlook—and to some extent, the outlook of its investors—beyond the next decade, as Microsoft did. "That's how you build continued sustainable growth."

Genzyme can already reasonably lay claim to some fairly radical moves, not least those creative financial engineering experiments that stretch back to the company's earliest years. When Wyzga arrived a decade ago, Genzyme had four separately listed tracking stocks, seven joint ventures, and 50% of a joint venture with spin-off Genzyme Transgenics (now **GTC Biotherapeutics Inc.**). [W#199330113] So for Genzyme, adapting to the future means maintaining that creativity and flexibility, while at the same time growing larger—closer in size to a mid-sized or even large pharma. There'll be no return to tracking stocks, Wyzga predicted. "Instead, we're creative in how we put deals together."

Evolutionary change, then, not revolutionary; and this driven as much by the dealmaking teams, it seems, as the bean counters. Indeed, the boldest signs of Big Pharma change during PSO sessions were probably from Jim Cornelius, **Bristol-Myers Squibb Co.**'s CEO. He acknowledged BMS' willingness to acquire: "If he can get his list together," Cornelius said, motioning toward his SVP, external science, technology, and licensing Jeremy Levin, MD, sitting in the audience, "then we're ready to act" on the company's so-called "string-of-pearls strategy" to acquire new technologies and capabilities, as demonstrated by the \$505 million acquisition of next-gen antibody play **Adnexus Therapeutics Inc.** in September 2007. [W#200710142]

But more interestingly, in describing this once-big-but-now-midsized pharma's planned metamorphosis into a next-generation biopharma firm, he talked openly about shrinkage--the 50% cut in sales force that's already happened since 2000, and the further 15% planned reductions over the next three years, not to mention the anything-goes-that-isn't-core-biopharma mentality. "Our total sales force for our recently launched breast cancer drug **Ixempria** is 125," he stated. Compare that with the 1,500-strong **Plavix** sales force--which, incidentally, may be out of a job by the end of 2011 when generics hit.

Perhaps this in itself--pharma talking about down-sizing rather than merger-mediated up-sizing--is transformation enough.