Critics say a conflict of interest couldn't be more clear, but the FDA doesn't think so.

COMPANIES RUN TRIALS OF DRUGS THEY INVEST IN

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Like many startup businesses, Accentia BioPharmaceuticals of Tampa was long on dreams but short on cash.

It held the license to an experimental sinus drug that looked like a potential blockbuster. But the company needed serious bucks to get the product to market.

Accentia found an investor in PPD Inc., a company that specializes in running the studies that must be conducted before regulators can approve a drug.

A year after recruiting PPD as an investor, Accentia went looking for someone to run the all-important trials proving the safety and effectiveness of its sinus drug.

Guess who got the job.

Now PPD is not only the second-biggest investor in Accentia, it also is handling the final preapproval studies of Accentia's new drug, SinuNase.

If the PPD-run trials result in the drug being approved by the Food and Drug Administration, financially strapped Accentia will be on its way to tapping a billion-dollar market of folks with chronic sinusitis. And PPD will get 14 percent of the royalties.

Is that a conflict of interest?

The FDA doesn't think so.

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The agency requires doctors to disclose any financial interest in drugs they are testing on patients, but it doesn't even gather such information from companies like PPD.

Charged with protecting the public, the FDA gets most of its drug approval budget from pharmaceutical companies. Increasingly, those companies have been foisting off the drudgery of running drug trials onto companies like PPD, which are called contract research organizations.

But now, instead of just being paid to conduct a study, some CROs are taking a stake in a trial's success. This does not concern the FDA's senior adviser for clinical science, Dr. David LePay.

"We assume CROs have a financial interest in the compounds they're testing," he said.

As proof the system is working, LePay noted how rarely the government finds fraud in clinical trials: "We only find it in 1 to 2 percent of inspections."

Others say those numbers prove something altogether different: that the regulators' focus is on approving, not challenging clinical studies.

"The FDA does not have the resources to inspect all clinical trial sites or even a major fraction of them," said Dr. David Ross, who was with the agency's drug review office for a decade. "And if you don't look for fraud, you won't find it."

Arthur Caplan, professor of bioethics at the University of Pennsylvania, said federal regulators need to pay more attention to contract research organizations. Even if they don't invest in a drug under review, the companies have an incentive to get patients enrolled and tests completed fast, he said. Timely, trouble-free trials are the ticket to the next contract.

"CROs stay in business by hitting the numbers," Caplan said.

And when a trial monitor has a financial interest in a drug study's outcome, as PPD does with SinuNase: "That's a big ethical no-no," Caplan said. "They should never be reviewing anything in which they have a direct financial interest."

Dr. Sidney Wolfe, director of the health research group at Public Citizen, a consumer group based in Washington, says it is common sense.

"The more things go in the direction of encouraging financial conflicts of interest," he said, "the more likely the decisions will go in a direction that is not in the interest of public health."

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Most preapproval drug testing used to be done in academic institutions, directly under the control of the drug companies. Now most trials are performed in regular doctors' offices around the globe, and contract research organizations handle a major chunk of the work. As hired hands for the pharmaceutical industry, last year the companies generated some $15-billion in revenue.

Head and shoulders above the competition in terms of size are PPD and its chief rival, Quintiles Transnational Inc. Together their more than 25,000 employees oversee thousands of clinical trials in more than 50 countries.

The two companies have distinguished themselves by offering clients a particularly attractive feature: money.

PPD, with $1.3-billion in revenue last year, has made four investments, including the one with Accentia. Through these "compound partnering" alliances, PPD said that last year it reaped $94-million in related clinical trial business. The company declined to comment for this story.

Quintiles, with $2-billion in revenue last year, started investing in up-and-coming drugs in 1999. Last year the investment division, called NovaQuest, teamed with a giant $5.8-billion venture fund to give it access to additional capital to invest. To date, NovaQuest has committed $2-billion to dozens of partnerships, including 26 deals with small biotechs.

Ron Wooten, the 49-year-old president of NovaQuest, said his company deals with the same potential conflicts of interest a drug company has when it oversees trials of compounds it owns.

"You manage that conflict by having fire walls around all information and strict confidentiality across all functions," he said. "Nobody on my staff talks to operations about there being higher stakes in a program when we have an investment. That never happens."

Nor is it in NovaQuest's interest to drag out trials on compounds that don't look promising, Wooten said.

"If safety signals are negative, we want to discontinue a trial as quickly as possible," he said. "As an investor we realize that safety issues absolutely diminish commercial opportunities."

Dr. Marcia Angell, senior lecturer at Harvard Medical School, doesn't buy it. She said having drug companies or their proxies in charge of drug trials means the entire system is corrupt, "from stem to stern."

"It's a house of cards built on a fundamental conflict of interest," said Angell, former editor of the New England Journal of Medicine and author of The Truth About the Drug Companies: How They Deceive Us and What to Do About It.

"The problem is that drug companies have inordinate influence over the evaluation of their own products. That, on the face of it, doesn't make sense."

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At the recent Partnerships with CROs conference in Orlando, Bob Eubanks hosted a special version of The Newlywed Game in the exhibit hall and former Olympic skating champion Scott Hamilton gave a saccharine keynote speech.

More than 1,500 attendees trolled the hall, where 200 exhibitors handed out chocolate bars and stress balls. In brochures, booth graphics and seminars, one theme resounded: When it comes to moving drugs to market, time is money.

At a workshop on accelerating study activities, Brenda Muldrow, vice president of INC Research Inc., set the tone: "Speed is key."

Nearly lost in the shuffle at the end of the conference was a session on ensuring quality data.

Brett Bishop, executive director of clinical operations at Covance, a large CRO, flashed a picture of a train wreck and gave the smattering of listeners who had not yet dashed for a plane a sobering account of the reality of today's clinical trials.

The accelerated development of trials has increased the risk of errors, Bishop said. There are more sites per study, less selectivity about sites, rushed study design and heated competition for patients.

Bishop showed a picture of an iceberg, likening it to clinical trials in which most problems are hidden from view.

"Protocol violations are much more common than data suggest," he said, referring to errors in the conduct and reporting of clinical trials. "They have an underestimated impact on drug development. They are not readily detectable. And conventional measures (to prevent them) are ineffective."

Nobody in the audience questioned Bishop's scathing assessment of the status quo.

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As the founder of CenterWatch, a company that tracks clinical trials, Ken Getz has watched the CRO business evolve over the past two decades, and he's a believer.

After selling CenterWatch, Getz became a senior research fellow at Tufts Center for the Study of Drug Development in Boston. In a report last year analyzing 83 clinical trials, Getz concluded that studies run by contract research organizations are completed faster and with comparable quality to those run by drug companies.

"There are isolated examples" of problems, he said. "But for the most part, CRO-run trials are run well, according to procedures."

Getz suggested that the companies serve an important oversight function because their monitors visit clinical trials while they are in progress. Federal regulators seldom make such site visits.

Getz said this puts contract research organizations in a unique - and what critics might say is an overly cozy - relationship with regulators. "What I find is the FDA relies on CROs to act as a kind of affiliate, since they're the ones monitoring the sites," Getz said.

CROs like being portrayed as independent watchdogs over the drug-testing process, even when the biggest players are becoming more financially involved.

When a recent report in the journal Cancer concluded that clinical trials supported by pharmaceutical companies were more likely to report positive findings than trials without their backing, the chairman of the CRO trade association used it as an opportunity to promote his industry.

"Even if one argues that pharmaceutical companies have a vested interest in trial results, it's important to note that CROs do not," Jeffrey McMullen, chief executive of PharmaNet, wrote on the trade group's Web site.

"Their obligation is to ensure data integrity and compliance with FDA and international regulations - period."

McMullen did not return phone calls seeking comment on PPD and Quintiles' investing activities.

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Dr. Francis O'Donnell, an ophthalmologist who is Accentia's chief executive and largest shareholder, said getting PPD to give his struggling Tampa company both cash and clinical trial services for its sinus medicine was a godsend.

"We needed to mobilize capital and we didn't want to surrender our commercial rights to the drug, like we would have had to have done with a big pharmaceutical partner," O'Donnell said of Accentia's deal, which trades PPD's services for future royalties on SinuNase.

"Their execution has been flawless, and their counsel has been invaluable to us."

Working from an office suite on South Hyde Park Avenue in Tampa, O'Donnell has spent three years pushing SinuNase and two other compounds through the drug approval process. In a presentation to investors last week, O'Donnell said results have been encouraging from the SinuNase trial, which involves more than 300 patients at 50 sites; final data are expected by year's end.

O'Donnell said there is no reason to think PPD's financial interests will affect its handling of the SinuNase trials.

"There are enough checks and balances built into the system," Accentia's chief said. "The chances of mischief are de minimis."

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FAST FACTS

CROs

- The top 10 contract research organizations control 80 percent of the market.

- In 2004, leading CROs managed 23,000 studies, conducted at more than 150,000 sites, involving more than 640,000 subjects.

- About 50,000 clinical trials are now taking place in the United States.

- One in eight doctors currently serves as a clinical investigator.

- 90 percent of clinical trials miss enrollment time lines and key milestones.

Sources: Tufts Center for the Study of Drug Development; Thomson CenterWatch 2005 survey of investigative sites; Interactive

Caption: PHOTO (4): Dr. Sydney Wolfe Arthur Caplan Ron Wooten Dr. Marcia Angell

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