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As drug industry's influence over research grows, so does the potential for bias

By Peter Whoriskey, Published: November 24

For drugmaker GlaxoSmithKline, the 17-page article in the New England Journal of Medicine represented a coup.

The 2006 report described a trial that compared three diabetes drugs and concluded that Avandia, the company's new drug, performed best.

"We now have clear evidence from a large international study that the initial use of [Avandia] is more effective than standard therapies," a senior vice president of GlaxoSmithKline, Lawson Macartney, said in a news release.

What only careful readers of the article would have gleaned is the extent of the financial connections between the drugmaker and the research. The trial had been funded by GlaxoSmithKline, and each of the 11 authors had received money from the company. Four were employees and held company stock. The other seven were academic experts who had received grants or consultant fees from the firm.

Whether these ties altered the report on Avandia may be impossible for readers to know. But while sorting through the data from more than 4,000 patients, the investigators missed hints of a danger that, when fully realized four years later, would lead to Avandia's virtual disappearance from the United States:

The drug raised the risk of heart attacks.

"If you looked closely at the data that was out there, you could see warning signs," said Steven E. Nissen, a Cleveland Clinic cardiologist who issued one of the earliest warnings about the drug. "But they were overlooked."

A Food and Drug Administration scientist later estimated that the drug had been associated with 83,000 heart attacks and deaths.

Arguably the most prestigious medical journal in the world, the New England Journal of Medicine regularly features articles over which pharmaceutical companies and their employees can exert significant influence.

Over a year-long period ending in August, NEJM published 73 articles on original studies of new drugs, encompassing drugs approved by the FDA since 2000 and experimental drugs, according to a review by The Washington Post.

Of those articles, 60 were funded by a pharmaceutical company, 50 were co-written by drug company employees and 37 had a lead author, typically an academic, who had previously accepted outside compensation from the sponsoring drug company in the form of consultant pay, grants or speaker fees.

The New England Journal of Medicine is not alone in featuring research sponsored in large part by drug companies — it has become a common practice that reflects the growing role of industry money in research.

Years ago, the government funded a larger share of such experiments. But since about the mid-1980s, research funding by pharmaceutical firms has exceeded what the National Institutes of Health spends. Last year, the industry spent $39 billion on research in the United States while NIH spent $31 billion.

The billions that the drug companies invest in such experiments help fund the world's quest for cures. But their aim is not just public health. That money is also part of a high-risk quest for profits, and over the past decade corporate interference has repeatedly muddled the nation's drug science, sometimes with potentially lethal consequences.

Over a decade, controversies over blockbuster drugs such as Vioxx, Avandia and Celebrex erupted amid charges that the companies had shaped their research to obscure the dangerous side effects.

When the company is footing the bill, the opportunities for bias are manifold: Company executives seeking to promote their drugs can design research that makes their products look better. They can select like-minded academics to perform the work. And they can run the statistics in ways that make their own drugs look better than they are. If troubling signs about a drug arise, they can steer clear of further exploration.

Maybe the most widely reported research controversy arose over the arthritis drug Vioxx, which had been featured positively in a NEJM article. The article reported the results of a trial that was funded by Merck and was co-written by two company researchers.

Five years later, journal editors reported discovering that the authors had omitted key incidences of heart troubles, creating "misleading" conclusions about the drug's safety. Before the drug was pulled from the market, according to a review by an FDA investigator, it caused an extra 27,000 heart attacks and cardiac-related deaths.

Other industry-funded papers published in NEJM have led to conclusions that were later contradicted. Research published in NEJM regarding bestsellers such as the anemia drug Epogen and heart drug Natrecor has been challenged later by studies performed by other researchers.

"Unfortunately, the entire evidence base has been perverted," said Joseph Ross, a professor at Yale Medical School who has studied the issue.

Just because industry-funded researchers arrived at conclusions that were later discarded does not mean that money biased their findings. Researchers get things wrong for lots of reasons — errors are a part of science.

But Ross notes that corporate bias can be particularly strong. The odds of coming to a conclusion favorable to the industry are 3.6 times greater in research sponsored by the industry than in research sponsored by government and nonprofit groups, according to a published analysis by Justin Bekelman, a professor at the University of Pennsylvania, and colleagues.

Moreover, at the same time that companies have been funding a larger share of research, they have shifted the job of conducting trials away from nonprofit academic hospitals to for-profit "contract research organizations." Critics say that with this change, corporate bias is less likely to be challenged.

Academics have "contributed to the quality, intellectual rigor, and impact of . . . clinical trials," the editors of the nation's top medical journals, including NEJM, wrote in an editorial in 2001. "But, as economic pressures mount, this may be a thing of the past."

With the for-profit companies competing to run the trials, "corporate sponsors have been able to dictate the terms," the editorial said.

In recent years, more than half of the money the industry spends on outside research goes to for-profit organizations rather than universities and other academic centers.

"It used to be that drug companies would hand their new drug over to an academic center to have it

tested, and then they sat back and waited," said Marcia Angell, who retired as editor in chief of NEJM in 2000 after more than 20 years at the publication. "Now they're intimately involved in every step along the way, and they treat academic researchers more like hired hands."

The result, Angell said, is that the research can be biased and that it can be difficult for medical journals to unmask the problems.

"I used to think that if studies were subject to rigorous peer review it would then be enough to simply disclose authors' commercial ties," she said. "But I no longer believe that's enough. It's too hard for anyone — editors, peer reviewers, readers — to tell whether that bias has affected the work."

The review process

Caught in the middle of this vast shift are the editors of the New England Journal of Medicine, which is owned by the nonprofit Massachusetts Medical Society and runs on advertising, subscriptions and other revenue.

More than 600,000 people in 177 countries read it each week, according to the journal's Web site, and it influences the practice of medicine around the world.

"Overall, we're in the business of trying to make people better," said Editor in Chief Jeffrey M. Drazen, who is also a Harvard Medical School professor.

The journal receives about 5,000 submissions a year. Those are reviewed by a staff of 10 editors — nine physicians and a geneticist — in addition to another 10 editors on contract.

Once an article makes the first cut, the article is sent to "peer reviewers" — the journal has an index of more than 10,000 such people — to scrutinize the reports. The reviewers typically assess the paper based on what is presented — they do not see all the data — but they often can tell when researchers are overstating their drug discoveries.

"We spend a lot of our time reworking language indicating that a drug is a blockbuster, when in fact the data show it's just so-so," Drazen said.

As the industry's influence has grown, the journal and Drazen, who arrived at NEJM in 2000, have repeatedly taken steps to root out commercial bias.

In 1984, the editors laid out a policy calling for authors to disclose their funding and financial associations. In 2001, they asked for more details about the company's role in the research. Then, last year, Drazen and his team required that the lengthy "protocols" of studies also be published, so anyone can see the exact steps that were taken.

Medical journals have also acted in concert. In 2004, Drazen and editors at other journals made it much harder for companies to hide unflattering experiments, requiring drugmakers to register a summary description of their trials in a public database.

"The drug companies went nuts about requiring registration," Drazen said. "They said, 'That's secret information.' We said, 'That's bull----.'

"As a group, we stood them down," Drazen said.

Despite such measures, medical science appears to have reached a crisis: Doctors have grown deeply skeptical of research funded by drug companies — which, as it happens, is most of the research regarding new drugs being published in NEJM.

According to a survey published this fall in NEJM, doctors are about half as willing to prescribe a drug described in an industry-funded trial. That's unfortunate, doctors say, because a good portion of the industry-funded research is done well.

"On the one hand, there are a lot of important industry-funded studies that are accurate, relevant and useful," said Jerry Avorn, a Harvard professor who has specialized in spotting adverse events from drug use. "There is also a multi-year history of abuse and distortion."

Responding to that skepticism, Drazen has urged doctors to overcome their doubts and to "believe the data," as he put it in a recent editorial.

"Some people thought I was a little naive" for saying that, Drazen said. But he said he is convinced that most researchers are on the same mission he has for the journal — to find the truth and help patients.

"This is a business built on people telling the truth," he said.

But Drazen said he has no illusions about what the demand for profits can do to pure motives. He noted that the stakes are highest for patients.

"I lie awake at night because I know somebody somewhere is trying to pull a fast one on me," he said. "Have we plugged every leak?"

He pauses and shrugs:

"We don't know. But we think we get most of them."

Risks vs. benefits

The outlines of the Avandia case — in which the drug's dangers had been recognized within the company long before the FDA pulled it from retail shelves — are well known.

But the way that company officials employed academics — and the prestige of the nation's top journal — to promote the idea that the drug was safe has received little public scrutiny, and a full account offers a window into the corporate decisions underlying today's drug research.

Interviews, FDA documents and e-mails released by a Senate investigation indicate that GlaxoSmithKline withheld key information from the academic researchers it had selected to do the work; decided against conducting a proposed trial, because it might have shown unflattering side effects; and published the results of an unfinished trial even though they were inconclusive and served to do little but obscure the signs of danger that had arisen.

The company says it acted properly throughout.

"We firmly believe we acted responsibly in conducting the clinical trial program, in marketing the medicine, in monitoring its safety once it was approved for use and in updating information in the medicine's labeling as new information became available," the company said in a statement.

From nearly the beginning, Glaxo scientists confronted signs of potential heart dangers in Avandia. In 2000, about a year after the drug's approval, a small internal study suggested that Avandia might raise "bad" cholesterol levels more than a competitor.

The company considered sponsoring a full-blown trial to weigh the issue, but before it did, scientists conducted a "risk/benefit" analysis — not to calculate the risks and benefits of the drug to patients but to see whether a full-blown trial could harm the drug's reputation.

When that analysis showed a sign of danger — Avandia raised bad cholesterol levels more than the competitor — the company decided to drop the subject.

"The study results support a 'no-go' decision," the internal report concluded, meaning that a full trial would not be conducted.

The researchers even warned one another against sharing the results of the preliminary study.

"Per Sr. Mgmt request, these data should not see the light of day to anyone outside of GSK," said an internal e-mail that was widely reported after it turned up in the Senate investigation.

Even when the company was ordered by the FDA to study potential dangers, it arranged a trial in which danger signs were muffled, or missed completely.

In approving Avandia, the FDA had asked the company to conduct a trial, known by its acronym ADOPT, to look into the drug's safety, including "cardiovascular events."

As is common practice, the company arranged for a group of experts — mostly academics — to form a steering committee to guide and publish the experiment. Four of the 11 committee members were Glaxo employees. The other seven reported serving as paid consultants or had other financial connections to the company.

The trial would involve more than 4,000 diabetic patients. About one-third would be given Avandia, the rest one of two older, commonly used drugs.

But as the FDA later noted, the ADOPT trial was not really designed to assess heart risks. For one thing, it excluded people most at risk of heart trouble, making it harder to spot a problem. Moreover, investigators did not have a group of doctors validate reports of heart attacks, as is customary because they can be difficult to detect. Finally, about 40 percent of patients dropped out of the trial.

These aspects of the trial "limited any ability" to draw conclusions about the risk of heart problems, an FDA staff memo later said.

Why would the academics have set up a trial like that? One reason is that Glaxo apparently did not tell its own academic researchers that the FDA had requested that the ADOPT trial look at possible heart troubles.

"We have no first-hand knowledge of what the FDA requested of [Glaxo]," Steven Kahn, a professor of medicine at the University of Washington and the lead author of the NEJM article, wrote via e-mail in response to Post questions. "ADOPT was clearly not designed to assess cardiovascular risk."

Moreover, as the academics were wrapping up their work and preparing it for publication in NEJM, Glaxo apparently did not inform their researchers of warning signs regarding Avandia and cardiovascular troubles.

"Up to the time that our paper was published, we were unaware of any concern that [Avandia] might potentially have adverse effects on cardiovascular disease," the seven authors who were not Glaxo employees wrote in an e-mailed response to Post questions. They stressed their belief that the results were fully presented.

The company, however, was aware of potential dangers.

In 2003, the Uppsala Monitoring Center of the World Health Organization had issued the company a warning that drugs of this type might be associated with heart trouble. Then, in 2005 and 2006, Glaxo conducted an examination of records from more than 14,000 patients and concluded that Avandia raised the risk of coronary blood flow problems by about 30 percent, the Senate investigators said.

The company contends, contrary to the authors, that it shared the findings of the 2006 study with the steering committee.

But in their article for NEJM, the authors focused mainly on the fact that Avandia had performed the best — that is, it was able to control blood sugar for the longest period.

As for those hints of cardiovascular risks that Nissen, the Cleveland Clinic cardiologist, had seen in the data? The authors pointed to no such trouble.

The risks of "cardiovascular events" associated with Avandia, the article said, were "similar" to those affecting patients who had taken metformin, one of the most prescribed diabetes drugs in the world.

The signal for doctors was clear: Don't worry.

'It didn't look right'

But Nissen could not help but worry.

He had seen other data that suggested to him that Avandia could cause heart trouble. Another trial sponsored by the company, known as DREAM, had shown a slight trend, he thought, but the number of patients was too small to be considered statistically significant. Then, in the ADOPT trial results, he saw the same clues repeated, even if they were not remarked upon by authors of the article.

The trend in the data was suggestive, Nissen thought, though again not statistically significant. In the two groups of patients that had taken the commonly used drugs, there had been 14 and 20 serious heart attacks. The Avandia group had 24.

And there was another clue: The measures of bad cholesterol were notably higher in the Avandia group.

"The trend was in the wrong direction, and that's what sent me off," Nissen said. "It didn't look right."

To see whether his suspicions were warranted, Nissen, with colleague Kathy Wolski, set out to assemble the data from every trial of Avandia that they could find. The more data they had, the more likely they could accurately gauge the risks. The drugmaker refused Nissen's requests for data, but because of litigation brought by Eliot Spitzer, then New York's attorney general, the company had been forced to make some of it public. In all, he discovered the summaries of 42 trials — 35 of them unpublished. Most of them had been sponsored by Glaxo.

After analysis, the results were stark: Avandia raised the risks of heart attack by 43 percent and of death from heart problems by 64 percent.

Those findings would stand up. But the reach of the pharmaceutical companies to influence the science would create three more years of uncertainty.

Glaxo ready to respond

Nissen and Wolski submitted their findings to NEJM on May 2, 2007.

Normally, an article takes several months to get published, but Drazen put it on a fast track, publishing it on the NEJM Web site 19 days later, on May 21.

"This was a big surprise, and I wanted to get it out there," Drazen said. "If it was right, thousands of people were having heart attacks because of this drug."

Glaxo was surprisingly well prepared to respond.

How? What was not known until later is that the NEJM paper had been leaked to the company.

As part of the process of peer review, the paper had been sent to Steven M. Haffner, a Glaxo ally and a University of Texas professor who had helped conduct the ADOPT trial.

Without telling Drazen or Nissen, Haffner faxed a copy of the confidential unpublished paper to the company, according to documents released by the Senate.

More than 40 company executives would learn of its contents. They prepared a meticulous response to its publication that suggested that Nissen's results were plain wrong.

"GSK strongly disagrees with the conclusions reached in the NEJM article, which are based on incomplete evidence and a methodology that the author admits has significant limitations," the news release said.

But internally, scientists and statisticians at Glaxo largely agreed with Nissen's calculations, the company e-mails released by the Senate show.

"To a great extent the numbers are the numbers, the Cleveland analysis is very similar to our own," one of them reported via e-mail.

An 'underpowered' study

The company would also launch one other strategic counter to Nissen's paper: They would publish the results of another, separate trial of Avandia that they were conducting, known as the RECORD trial.

One of the reasons that the Glaxo executives could be confident that the RECORD trial would show no danger is that the trial did not have enough patients enrolled to judge the drug's heart-attack risks, as Glaxo scientists believed, according to the Senate report. It was, in the scientific jargon, " underpowered."

The Glaxo executives faced one big problem, however. The RECORD trial was two years from completion. Publishing the interim results of a trial is very unusual because it tips off patients and doctors in a way that could bias results.

Like the ADOPT trial, the RECORD trial was funded by Glaxo, which had in turn hired a steering committee of prestigious academics to lead it.

The researchers in the RECORD trial had many financial ties to the company, too. Of the eight authors of the RECORD trial report, one was a Glaxo employee. The other seven reported having received consulting fees or other support from Glaxo. One, Philip D. Home, reported donating such money to medical institutions.

While the academics were nominally in charge of the trial, it would be the company, not the academics, who would first decide to publish the interim results.

The day before the academics were to meet, Ronald L. Krall, Glaxo's chief medical officer, told another employee in an e-mail, "We've decided we will disclose the results."

If the steering committee objected, the executives were prepared to tell them that a "decision has been made — live with it," according to an e-mail from Glaxo executive Trevor G. Gibbs.

When the academics were convened the next day, the group went along with the decision to publish interim results. They decided on their own, the steering committee's chairman, Home, said via e-mail. He said they feared that Nissen's warning could scare patients and doctors out of the trial, and they needed to reassure them.

"We had no choice but to publish," he said. "The decision was inevitable if regrettable."

In their first submission to NEJM, Home and his co-authors indicated that the RECORD trial results had undermined Nissen's warning, according to a letter from the journal to the authors.

But NEJM's peer reviewers noted that the data did not support that conclusion, and they demanded changes.

As result, when the article appeared in July 2007, it did not say anything definitive about Avandia and certain heart problems.

The paper said that the results of the RECORD trial were "inconclusive" as to whether the drug raised the risk of cardiovascular problems and that the data were "insufficient" to determine whether the drug raised the heart-attack risk.

Yet the language in the article, though equivocating, might still have helped Avandia sales by making the issue look like a muddle.

"What it did was it falsely reassured practitioners and patients that [Avandia] might be safe when in fact it wasn't," Nissen said. "They got three more years out of it."

It was not until 2010 that Nissen was largely vindicated. An FDA reviewer indicated that the RECORD trial had been poorly designed and suggested that investigators had improperly missed heart problems suffered by Avandia patients.

In September 2010, the FDA announced major restrictions on the use of Avandia. On the same day, European regulators ordered it off the market.

Blocking bias

In the wake of controversies arising around Vioxx, Avandia and Celebrex, many in the medical world have sought ways to ensure that drug research is free of commercial bias.

One of the leading proposals would be to compel drug companies to release all of the data from trials of drugs that are on the market.

Over the summer, the European Medicines Agency — the continent's counterpart to the FDA — said it will move toward requiring the release of all such data. Glaxo, too, has said it is preparing for such a release, though other companies have yet to follow suit.

"Since 2004, we have posted summaries of all our clinical trial results on our Web site for the world to see," Glaxo said in a statement. "All of these actions speak to the degree of commitment we have to be open with our research so there can be more understanding, and hopefully credibility, in what we are doing."

Such transparency about industry-sponsored trials would not eliminate the ability of companies to avoid unflattering studies, or to hire like-minded researchers, or to design research that gives only positive views of their products.

But if such measures are carried out across the industry — and there is no sign at this point that they will be — independent researchers could analyze the data from trials and come to their own conclusions.

Many believe drug companies should feel obliged to share such information.

"If you have the privilege of selling a drug, in return should come the responsibility to share everything you know about the drug," said Harlan Krumholz, a professor of medicine at Yale and a leading advocate of data access. "This is not about doing gotcha with industry. It's about how to restore trust."

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