

Sunshine on conflicts

US drug companies are preparing for new draconian provisions for reporting on financial relationships with academia. Will efforts to increase transparency prove burdensome to researchers and the industry? Virginia Hughes investigates.

In late May, the US National Institutes of Health announced a draft set of rules for managing conflicts of interest among its grantees¹. In late April, Senator Charles Grassley (R-IA) sent a stern inquiry to the Centers for Disease Control and Prevention in Atlanta following a government report claiming that the agency was lax in policing financial conflicts of interest between experts serving on advisory committees and the pharmaceutical and biotech industries². This is only the latest fallout from Grassley's long campaign for increased transparency between physician researchers and industry. Thanks to his efforts, the massive healthcare reform legislation passed in March includes provisions mandating that every pharmaceutical, biotech or medical device company disclose, on a publicly searchable website, all payments of \$10 or more made to physicians or teaching hospitals.

Some stakeholders contend that strict disclosure rules add unnecessary and unjust burdens to an already struggling biotech industry—particularly to fledgling companies with few sales. “One thing we can be absolutely, guaranteed sure about is that the industry's going to have to spend money to do it,” says Tom Stossel, director of translational medicine at Brigham and Women's Hospital, in Boston, and founder of a small biotech called Critical Biologics. “At a time when the biotechnology industry profitability is low and the investment ecosystem is completely seized up, is this what we want to throw money at?” he asks.

Push and pull

Industry and academia have a symbiotic relationship. The type of blue sky research that is undertaken in academia is typically too risky to be carried out in industry. But when researchers hit upon something clinically useful, they need companies to scale up their work, develop products and guide them through the long and expensive regulatory road. In return, industry gains access to innovative therapies, as well as to patients, a rigorous clinical trial infrastructure and the public relations bonus of being affiliated with distinguished universities and hospitals.

Eighty percent of clinical departments at US medical schools receive industry funding of some kind—from research support to

faculty lunches—according to a 2007 survey³. And the money seems to move things along: clinical trials are published eight to ten times faster when one of the investigators is affiliated with industry⁴.

Although customary now, financial entanglements between the two realms were practically nonexistent before 1980. That's when the Bayh-Dole Act deemed that companies, universities or nonprofits could own the intellectual property resulting from federally funded research, taking it out of the public domain. Suddenly, academic researchers and their institutions could apply for patents and license discoveries to companies. Many credit the act for the rapid rise of the US biotech industry.

Those relationships are growing more numerous, thanks to shrinking federal research budgets and industry's stagnant product pipeline. In the past two years, big pharma has forged a dozen multi-million dollar research collaborations with prominent medical centers.

Industry is particularly valuable in nascent fields that require expertise in several areas of biology, such as stem cells, notes Brock Reeve, executive director of the Harvard Stem Cell Institute in Cambridge, Massachusetts. He estimates that 40–50% of the institute's budget comes from industry. “To do research in a multidisciplinary area like stem cells, no one company, and no one lab, is going to have all the necessary resources,” Reeve says. “These relationships are critical to innovation.”

The hitch is that what's best for a company isn't always what's best for patients. And doctors who are paid consultants can sometimes have a hard time managing these competing interests. Some studies suggest that physicians who receive research funding, honoraria, gifts or meals from industry are more likely to prescribe newer, more expensive drugs, even when an effective

generic is available⁵. A survey of authors of clinical practice guidelines—which outline standard treatments and influence the decisions of many physicians—found that 38% had been pharmaceutical company consultants and 58% received research support from industry⁶.

In addition to prescribing patterns, clinical research may be biased as well. For example, a report evaluating 1,140 papers published between 1980 and 2002 found that industry-sponsored studies are more likely to yield results that benefit the company⁷. Another review analyzed data submitted to the US Food and Drug Administration (Silver Spring, Maryland) for 74 clinical trials of 12 common antidepressants. In roughly half of the trials, the FDA deemed the drug effective. Only 51 studies were published ever, and 48 of them (94%) were reported to have positive results⁸.

Culture shift

The issue hit the headlines in June 2008, when the *New York Times* reported that Senator Grassley's investigators had found large discrepancies between what pharmaceutical companies said they paid three Harvard psychiatrists and what those researchers actually disclosed to the university. Each reported only a fraction of the more than \$1 million received through various company relationships. Grassley's team has since found similar inconsistencies in disclosure statements from dozens of other academic researchers. Subsequent surveys of physicians suggest that these aren't isolated cases.

For example, a study published in the *New England Journal of Medicine* analyzed disclosure statements submitted by physicians who presented work at the annual meeting of the American Academy of Orthopedic Surgeons, and compared the payment figures to those published on device

manufacturers' websites (**Box 1**). Only 71% of payments were disclosed⁹.

“There probably is a minority of surgeons who intentionally did not disclose, but I think a large part of it is that the disclosure requirements are so confusing,” says lead investigator Mininder Kocher, associate professor of orthopedic surgery at Harvard Medical School in Boston. Kocher, who serves as a surgical consultant to the orthopedics industry, says that these relationships are common and necessary. “But they clearly also have the potential to be



It's official. With the passage of the health care reform act came new mandates for reporting industry/academia partnerships. (Source: The White House)

negative. So the solution that's most commonly advocated is disclosure."

There is some debate, however, as to whether disclosure rules should be mandated by the federal government. "You can't legislate morality," says Peter Corr, co-founder of Celtic Therapeutics, a biotech investment company located in the US Virgin Islands, and former head of worldwide R&D at Pfizer. Last year, Corr sat on an Institute of Medicine committee on conflict of interests in medicine, which published a report urging the professional community to create a "culture of accountability."

Corr says that any legislation that impinges on the relationship between industry and academia is problematic. "I would hope that the profession can police itself," he says. "Otherwise, I think the government will end up doing things with unintended consequences that would be sad for society as a whole."

Others counter that because it helps to protect consumers, physician disclosure is a government matter. "Transparency is necessary for patients and the public to be able to assess the relationships and be fully informed," says Allan Coukell, director of the nonprofit Pew Prescription Project in Washington, DC. "While this is a pure transparency bill, we hope that it will continue to help the process of culture change that's already underway," he adds.

Federal moves

The stories of highly paid physician consultants certainly got the public's attention, and paved the way for Grassley and fellow Senator Herb Kohl (D-WI) to introduce the Physician Payment Sunshine Act in January 2009. The act was later folded into the healthcare reform legislation passed earlier this year. Companies must start recording payments on January 1,

2012, and submit their first annual report to the department of Health and Human Services by March 31, 2013. The information will appear on a public website—searchable by physician name—by September 30, 2013. For each payment of \$10 or more, companies must record the form of the payment (cash or stock), the nature of the payment (gift, royalty, consulting fee) and, if applicable, the drug or device that's related to the payment.

Providing this detailed accounting was of foremost concern to doctors who consulted with Grassley's team during the development of the legislation. "If the reporting lumps all of the payments into one, and lacks context, it can create a false impression. A lunch is different from a royalty is different from a research project," notes Christopher Armstrong, investigative counsel to the Senate Committee on Finance, who wrote most of the bill's language. Armstrong talked to hundreds of physicians and industry representatives when putting the bill together.

The provisions also mandate that companies report contributions to research. But to ensure intellectual property, research support does not have to be disclosed for four years, or until the product is approved, whichever comes first.

Jumping on the disclosure bandwagon, several large companies have already set up their own websites listing physician payments. Eli Lilly of Indianapolis, and Pfizer were required to, as part of the terms of legal settlements with the federal government over illegal marketing of drugs. Their websites, however, are often difficult to navigate and don't specify what the payments are for (Table 1).

So far, six state legislatures—in the District of Columbia, Maine, Massachusetts, Minnesota, Vermont and West Virginia—have passed disclosure rules. Four apply only to drug compa-

nies, and three require that the information be made public. Publicly available databases have been set up by the Attorney General of Vermont (<http://www.atg.state.vt.us/issues/pharmaceutical-manufacturer-payment-disclosure.php>) and the Minnesota Board of Pharmacy (<http://extra.twincities.com/CAR/doctors/>). According to Michael Gonzalez-Campoy, CEO of the Minnesota Center for Obesity, Metabolism and Endocrinology, a private institution outside of St. Paul that conducts industry-sponsored research, many medical institutions in the state have banned interactions between their physicians and industry. This has made recruiting top talent difficult owing to the hostile environment created by Minnesota's law, he says.

One justification for creating a federal database is to standardize the reporting from all of these preexisting sites, according to Armstrong. The federal legislation preempts all state disclosure laws, unless the state requires information that is not covered in the federal laws. "If the information is all in one place, companies have one rule to follow, not 80 rules, and the public only has one website to consult," Armstrong says.

Industry reactions

In a 2008 statement, industry group Pharmaceutical Research and Manufacturers of America, located in Washington, DC, came out in favor of disclosure and praised the Sunshine Act for superseding local legislation. The "confusing myriad" of state rules, it said, are "overly burdensome and costly for those required to report." But although the additional costs of conforming to the legislation might not be burdensome to big pharma, they certainly will represent a drain in time and money for smaller companies. For now, the biotech industry's lobbying group, the Biotechnology Industry Organization, also based in Washington, DC, is sitting back. "We'll monitor their implementation and weigh in with the designated agency as appropriate," says general counsel Thomas DiLenge.

Leaders of Adolor, a biopharmaceutical company in Exton, Pennsylvania, say they welcome increased transparency, but also point out that complying with the new legislation will affect their business operations. "It will be necessary to allocate resources to purchase the systems to track these criteria and dedicate personnel to manage the process," notes Eliseo Salinas, senior vice president of R&D at Adolor. "This expense will, unfortunately, shift dollars away from our ongoing drug development programs."

But Kay Dickersin, director of the Center for Clinical Trials at Johns Hopkins University in Baltimore, says that's just part of the cost of doing business. "It's like saying you have to have an office, or a lawyer," she says.

Box 1 Orthopedics' disclosure drama

The medical device industry has found itself at the center of conflict of interest storms because unlike drugs, orthopedic devices are often invented or modified by surgeons. "A lot of advances we've had in orthopedics came from relationships between physician innovators and industry," says Mininder Kocher of Harvard Medical School, who consults with device companies.

But sometimes there's a downside to those interactions. The most well-known example occurred in March 2005, when US federal prosecutors began investigating five manufacturers of artificial joints for bribing doctors to exclusively use their products. The companies—Biomet, Smith & Nephew, Stryker Orthopedics, Zimmer Holdings and the DePuy Orthopedics unit of Johnson & Johnson—represent roughly 95% of the market for hip and knee implants.

The government investigated physician relationships forged as early as the late 1990s and brought formal charges against the companies in 2007. The companies settled for a combined \$310 million in penalties, although none admitted any wrongdoing.

Some say the settlement spurred interest in the new federal Sunshine provisions. "I'd say it was a pretty significant part of the motivation behind the [new] legislation," says Bill Kolter, of Biomet.

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Table 1 Companies' disclosure websites

Company/website	Earliest period reported	Data reported	Format/search ability
Eli Lilly http://www.lillyfacultyregistry.com/Pages/index.aspx	Q1–Q4 2009	Doctor payments for consulting and speaking only	Flash website, not downloadable or searchable
GlaxoSmithKline http://gsk-us.com/docs-pdf/responsibility/hcp-fee-disclosure-2q-4q2009.pdf	Q2–Q4 2009	Doctor payments for consulting and speaking only	PDF, extremely small font
Merck (Whitehouse Station, New Jersey) http://www.merck.com/corporate-responsibility/docs/business-ethics-transparency/APA_4Q09_Grant_Trans_Data_v15_051010.pdf	Q3–Q4 2009	Doctor payments for speaking only	PDF, extremely small font
Pfizer http://www.pfizer.com/responsibility/working_with_hcp/payments_report.jsp	Q3–Q4 2009	Lists doctors making a total of at least \$500. Lists individual payments of \$25 or more. Includes money for research collaborations	HTML, searchable by doctor name
Cephalon (Frazer, Pennsylvania) http://www.cephalon.com/our-responsibility/fees-for-services-2009/fees-for-services-2009.shtml	2009 calendar year	Lists total amount paid to individual doctors for speaking and consulting. Does not list individual payments	HTML, searchable by doctor name

The penalty for companies that unknowingly fail to disclose is up to \$10,000 per payment, not to exceed \$100,000 per year. For intentionally not reporting, the fines go up to \$100,000 per payment, with a \$1 million annual cap. Although big pharma might not have trouble complying with the new laws, some experts say that small companies and startups will take a hit. “Where it is a casualty is where a company has to have a full-time person who decides whether it’s OK to buy their collaborator lunch,” says Stossel. Last year, Stossel founded the Association of Clinical Researchers and Educators to advocate on behalf of physician–industry partnerships. “Companies that have sales can do it. But the companies that have few sales are going to have a terrible time with it,” he says.

Joel Martin, president and CEO of Altair Therapeutics, an eight-person company in San Diego, says the regulations are “incredibly stringent,” particularly for companies like his that are still in early development phases of their products. Altair is collaborating with several Canadian academic medical centers to carry out a phase 2 clinical trial.

It’s entirely possible, he says, that a strong backlash against pharma will cause more academics to bow out of industry relationships. “And if that happened, I would be tremendously disappointed. You don’t want drugs developed in a vacuum.”

This is exactly what happened to Velico Medical, a ten-person company in Beverly, Massachusetts. Velico CEO Doug Clibourn says that the company tried—and failed—to retain a renowned expert from an elite institution as a device consultant. “He would have had to go through enormous hoops,” to comply with his institution’s rules, Clibourn says. “We don’t even have a product, we’re just trying to figure out a product. But still he’s not able to talk with us.” For similar reasons, Velico no longer has a scientific advisory board, Clibourn says.

“We’ve operated in this universe for decades with an amazing synergy between the clinical community and companies that are developing new products,” he adds. “From our perspective, the ethical questions are sort of absurd.”

Public perceptions

For his part, Grassley does not deny that these relationships are essential for developing new medical treatments. But, he says, patients deserve to know about their doctors’ conflicts of interest, which the new laws will lay bare. “My work on the disclosure issue, since 2007, has focused on oversight of what is happening in the real world,” Grassley says.

A few doctors have already publicly stepped down from academic positions over conflict of interest rules. This January, for example, allergy specialist Lawrence DuBuske resigned from his clinical position at Brigham and Women’s Hospital—and lost his academic position at Harvard Medical School—after the partner institutions announced that they would no longer allow its doctors to be paid speakers for the pharmaceutical industry. DuBuske reportedly made \$99,375 last year from GlaxoSmithKline of London for giving 40 talks in three months, and has similar agreements with six other companies.

“Academia will be losing more and more smart people,” because of its growing anti-industry sentiment, says Antonio Hardan, associate professor of psychiatry at Stanford in Palo Alto, California, who has consulting and research relationships with several pharmaceutical companies. “You’re going to see more people deciding either to go straight into industry or to not do research at all.”

Thomas Sullivan, president of Rockpointe Corporation, a medical education company in Columbia, Maryland, takes it a step further. “This kind of anti-industry culture that’s being permeated is pretty rapidly moving research and

development, and even commercialization, into other regions of the world,” he says.

The laws perpetuate the myth among the general public that all doctor–industry relations are bad, says Gonzalez–Campoy. “A lot of harm comes from the implication that doctors are corruptible, that they don’t do what they think or know is best for their patients,” he says. He believes that there will be a “significant delay” in the implementation of new treatments in the US, and a growing number of drug developers going abroad.

But Tom Insel, head of the National Institute of Mental Health in Bethesda, Maryland, says the public’s disapproval of physician–industry relationships is precisely why disclosure laws are so important. “In terms of the ability at least to put everything in the public domain, and to try to restore public trust, this is a step in the right direction,” he says.

In the end, perhaps the best way to gain the public’s trust is to develop useful treatments—and not be shy about it, says Derek Lowe, a blogger and chemist in the pharmaceutical industry. “Overall, the laws are probably a good thing, because the less we look like we have something to hide, the better off we are.”

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