FEATURES

HIDDEN CONFLICTS?

An investigation finds a pattern of after-the-fact compensation by pharma to those advising the U.S. government on drug approvals

By **Charles Piller**; *Data analysis by* **Charles Piller** *and* **Jia You**

On a sweltering July day in 2010, seven medical researchers and one patient advocate gathered in a plush Marriott hotel in College Park, Maryland, to review a promising drug designed to prevent heart attacks and strokes by limiting blood clotting. The panel is one of dozens of advisory committees that vote each year on whether the Food and Drug Administration (FDA) should approve a therapy for the U.S. market. That day, panel members heard presentations on the drug's preclinical and clinical data from agency staff and AstraZeneca in Cambridge, U.K., its maker and one of the world's largest pharmaceutical companies. The occasion sparked little drama. In the cool refuge of the conference room, advisers politely questioned company scientists and complimented their work. By day's end, the panel voted seven to one to approve. FDA, as usual, later signed off. The drug, ticagrelor, marketed under the name Brilinta, sold rapidly, emerging as a billion-dollar blockbuster. It cuts risk of death from vascular causes, heart attacks, and strokes modestly more than its chief competitor—and currently costs 25 times as much.

FDA, headquartered in Silver Spring, Maryland, uses a well-established system to identify possible conflicts of interest before such advisory panels meet. Before the Brilinta vote, the agency mentioned no financial conflicts among the voting panelists, who included four physicians. As Brilinta's sales took off later, however, AstraZeneca and firms selling or developing similar cardiovascular therapies showered the four with money for travel and advice. For example, those companies paid or reimbursed cardiologist Jonathan Halperin of the Icahn School of Medicine at Mount Sinai in New York City more than $200,000 for accommodations, honoraria, and consulting from 2013 to 2016. During that period, Halperin got $7500 from AstraZeneca to study Brilinta, and the company separately declared nearly $2 million in "associated research" payments tied to him.

Brilinta fits a pattern of what might be called pay-later conflicts of interest, which have gone largely unnoticed—and entirely unpoliced. In examining compensation records from drug companies to physicians who advised FDA on whether to approve 28 psychopharmacologic, arthritis, and cardiac or renal drugs between 2008 and 2014, *Science* found widespread after-the-fact payments or research support to panel members. The agency's safeguards against potential conflicts of interest are not designed to prevent such future financial ties.

Other apparent conflicts may have also slipped by: *Science* found that at the time of or in the year leading up to the advisory meetings, many of those panel members—including Halperin—received payments or other financial support from the drugmaker or key competitors for consulting, travel, lectures, or research. FDA did not publicly note those financial ties.

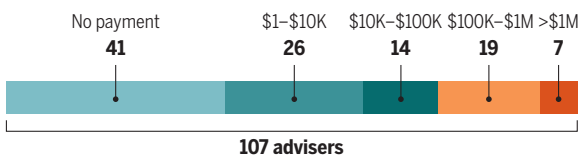
The analysis, which used physician disclosures in freely available publications and Centers for Medicare & Medicaid Services records for 2013 to 2016 on the federal Open Payments website, examined direct payments to physicians from firms whose drugs were voted on. It also considered payments from competitors selling or researching drugs of the same class or intended for the same condition—because competing drugs might be affected positively or negatively by the market entry of a new contender or by restrictions or warnings placed on a new drug's label. *Science* further looked at research funding from a company to an FDA adviser, directly or through their institution. Such money—including "associated research" funding that nearly always supports principal investigators—affects a scientist's career advancement, compensation, or professional influence.

Among the investigation's key findings:

- Of 107 physician advisers who voted on the committees *Science* examined, 40 over a nearly 4-year period received more than $10,000 in post hoc earnings or research support from the makers of drugs that the panels voted to approve, or from competing firms; 26 of those gained more than $100,000; and seven more than $1 million.
- Of the more than $26 million in personal payments or research support from industry to the 17 top-earning advisers—who received more than $300,000 each—94% came from the makers of drugs those advisers previously reviewed or from competitors.
- Most of those top earners—and many others—received other funds from those same companies, concurrent with or in the year before their advisory service. Those payments were disclosed in scholarly journals but not by FDA.

Varying sums

An analysis of pharma payments to 107 physicians who advised FDA on 28 drugs approved from 2008 to 2014 found that a majority later got money for travel or consulting, or received research subsidies, from the makers of the drugs on which they voted or from competing firms.



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Corporate payments and other support given to advisers before a drug review are widely acknowledged as troubling. When "a voting member of a committee demonstrably had financial associations with the company or the competitor prior to the meeting, and the FDA doesn't flag it, then somebody's dropping the ball on due diligence," says Yale University physician Robert Steinbrook, editor at large for *JAMA Internal Medicine*.

Yet benefits that come later, even years after a drug approval vote—jobs, money, professional prestige, and influence—are also fraught, ethicists say. They are a way of "postponing your reward," says Carl Elliott, a medical ethicist at the University of Minnesota in Minneapolis who has persistently criticized the financial inducements pharma gives to researchers (*Science*, 23 May 2014, p. 793). "You do something positive for a company that you feel confident is going to pay you back for it later on. And they do."

Vinay Prasad, a hematologist-oncologist at Oregon Health & Science University in Portland who has studied financial conflicts in drug approvals, is similarly troubled. "The people who are asked to weigh this evidence impartially often stand to gain tremendously in their further professional careers from a positive relationship with the company," he says. It might not be a "quid pro quo," according to Prasad, "but you don't have to evoke that to be very concerned. It's in their best interest to play nice with these companies."

FDA declined interview requests about *Science*'s findings. A spokesperson provided a statement saying people serving on drug approval advisory panels must disclose any "prospective employer," but not anticipated payments. The statement further notes that "FDA also screens potential participants for relationships and situations that do not create a financial conflict of interest but that may create the appearance that a committee member lacks impartiality."

AstraZeneca spokesperson Karen Birmingham says "we are not aware" of any effort to support advisers after they serve on FDA panels reviewing the company's drugs, "other than the routine involvement in clinical trials or expert panels for which that [adviser] may have been sought independently because of their expertise."

Halperin says a direct payment from a drug company for a lecture or consulting "isn't really very much different than having an insurance company giving you a check for seeing a patient one day. It's the same thing." He adds that he did not personally benefit from more than $1.9 million in research funds that AstraZeneca declared. He says the funds were paid to Duke University in Durham, North Carolina, to support a major study of Brilinta and that his role was to chair its data monitoring committee. His 2009 recommendation for Brilinta's approval, he says, was not influenced by anticipation of large payments or research funding from AstraZeneca or its competitors. And Halperin argues that such relationships may be the price of expertise. "It's probably better to have someone who has some experience in [the specialized topics considered] than a bunch of unconflicted high school students," he says.

But the cardiologist agrees that expectations of future rewards can promote bias. "I share [the] concern that this could lead to people acting in ways that you would not want them to do," Halperin says. "We don't want incentives that are not serving the public interest. In my case, it's the patient's interest." And he notes that some medical organizations have begun to address delayed incentives. They ask members who write clinical practice guidelines to avoid financial relationships with affected companies for a period afterward—a tougher standard than what FDA requires for its advisers.

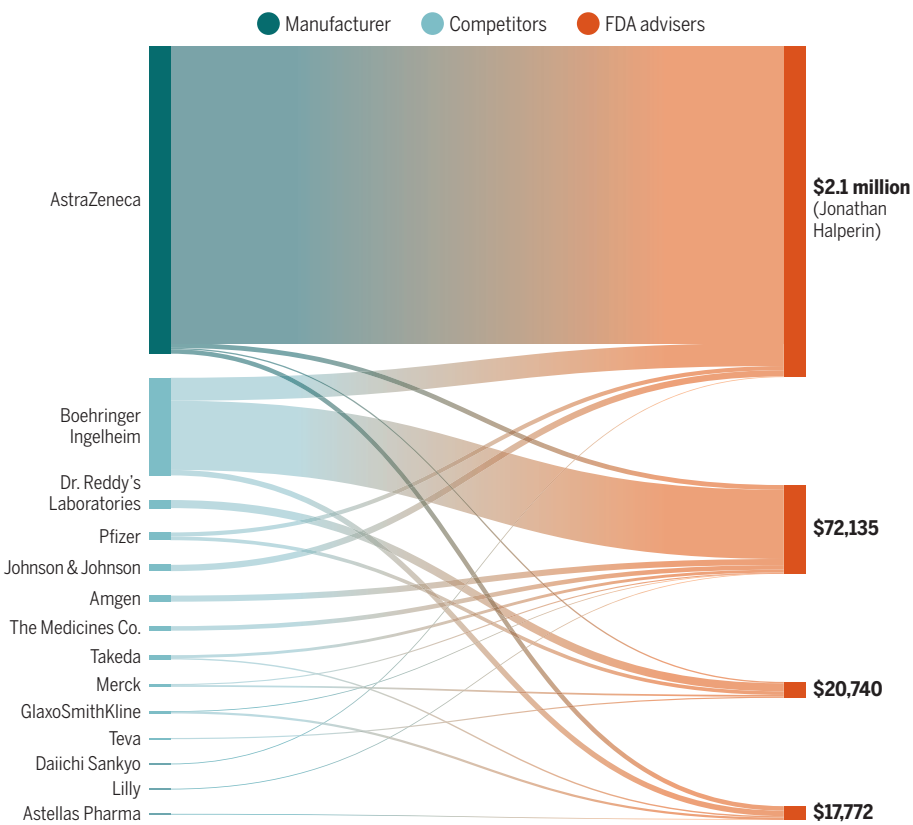
That solution and others should be up for debate, say ethicists and regulatory experts, including one prominent former FDA employee. "The idea of banning future payments is likely to have a lot of thorny aspects, but it's worth discussing," even at the risk of losing some experts to government service, says David Kessler, FDA commissioner under former Presidents George H. W. Bush and Bill Clinton. "It's a balancing act, but public trust is paramount."

JACOB SITKO ENLISTED in the U.S. Army in January 2008 and gave his heart and soul to it for more than 3 years—for a time serving in Iraq as a Humvee gunner in the infantry. In 2011, the private died in bed at his barracks at Fort Carson in Colorado, where he was being treated for posttraumatic stress disorder (PTSD). Months later, the Army finally gave Sitko's heart back to his mom.

Lois Vinall cries softly as she recounts her son's story. Right after his death, the Army told her that Sitko, who was 21 and in good health other than his PTSD, had been killed by "mixed-drug intoxication." Army doctors had been giving him a cocktail of medicines that included quetiapine,

After the Brilinta vote

In 2010, FDA advisers voted to recommend approval for Brilinta, which helps prevent blood clots in heart-disease patients. Four physicians who voted later received funds from AstraZeneca, its maker, and competing firms for consulting and travel, or worked on research underwritten by those companies.



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a top-selling antipsychotic from AstraZeneca sold under the name Seroquel. The particular mixture had been linked for years to sudden cardiac death, though no evidence has been made public that Sitko was told that.

"They sent his body home without his heart" and didn't say why, Vinall says. "They returned it in a baby coffin to me 3 months later, wrapped in green felt." Vinall recently learned that after removing her son's heart, the Army decided not to examine it further. She says a military medical examiner told her Sitko's autopsy hadn't been correctly "certified" and that her son might have suffered cardiac death. Vinall had cremated his body but buried his heart in a veterans' cemetery in Redding, California, close to family.

Two years earlier, two panels of FDA advisers had considered whether to approve Seroquel for new conditions—schizophrenia and bipolar disorder in children, and depression in adults who are taking other medicines. Seroquel was then known to be associated with sudden cardiac death when used with certain drugs, and several antipsychotics similar to Seroquel also had a record of cardiac fatalities. But AstraZeneca presented results from its clinical studies, which company representatives said showed, at worst, minimal risks (see sidebar, p. 21).

In 2009, both panels voted by wide margins to approve Seroquel for the additional conditions. In the years afterward, several FDA advisers received significant financial support from AstraZeneca and the makers of competing drugs. The biggest payments went to Duke cardiologist Christopher Granger, who sat on one of the two groups. From 2013 to 2016, the period recorded by Open Payments, he or Duke on his behalf received more than $63,000 from AstraZeneca and $1.3 million from competitors. According to conflict-of-interest disclosures in journal articles on which Granger was an author, he received additional, unspecified amounts from those companies between 2010 and 2012.

Granger says the industry funds solely underwrote research on cardiovascular topics and did not augment his salary. But according to the federal data, more than $400,000—including all of AstraZeneca's portion—went to him for travel, consulting, and honoraria.

"I fully realize that when I'm paid by somebody, like every other human being, that may affect the way that I think about things. So I'm not naïve," Granger says. But the expectation of future support from the makers of antipsychotics, he adds, did not influence his assessments of Seroquel or similar drugs. Granger says he recommended the drug's conditional approval after becoming convinced—as were nearly all others on his panel—that Seroquel's value outweighed its risks for some people with severe psychiatric disabilities.

The next year, in 2010, AstraZeneca paid the government $520 million to settle lawsuits involving alleged improprieties in the company's clinical trials and improper marketing of Seroquel for unapproved conditions. The company, which denied wrongdoing, pulled in more than $5 billion in revenues from the drug that year. In 2011, after mounting evidence of sudden cardiac deaths, FDA forced AstraZeneca to add a warning to Seroquel's label that the drug posed risks of fatal cardiac events when combined with certain other drugs. Sitko died 3 weeks later.

In recent years, FDA has fielded thousands of complaints about cardiac problems, including many deaths, tied to Seroquel. Granger calls the drug's widespread use for unapproved conditions, such as insomnia, a "public health tragedy." Sitko and many others were given the drug, in part, to treat insomnia. The company has said repeatedly that Seroquel is acceptably safe and effective to treat conditions for which FDA approved it.

> ***"I share [the] concern that this could lead to people acting in ways that you would not want them to do."***
>
> **Jonathan Halperin**, Icahn School of Medicine at Mount Sinai

POLICING FUTURE DRUG INDUSTRY payments received by FDA advisory committee members would be challenging even for an agency adept at limiting conflicts of interest. Yet *Science*'s investigation raises questions about how well FDA enforces more traditional conflict rules.

FDA asks panel members who vote on recommending drug approvals to disclose in advance details of investments, contracts, or other payments from drugmakers. The agency uses those disclosures to determine whether pharma backing during or before a meeting should disqualify an adviser. Each adviser must "certify to the truth and completeness of any information provided," according to the FDA statement to *Science*. The agency can issue a waiver to permit participation despite an active conflict or one that ended during the 12 months preceding a meeting if special expertise cannot readily be obtained otherwise. That system helps secure researchers with "deep scientific and medical expertise," Kessler, a pediatrician and lawyer now at the University of California, San Francisco, says.

But the agency's financial review process is primarily an honor system and seems to miss obvious conflicts. For the 17 physicians receiving the most compensation after a drug advisory vote, *Science* examined whether they also received industry compensation concurrent with or shortly before their FDA service. Evidence of such payments came from conflict-of-interest statements in journal articles that those authors published near the time of their advisory role. Eleven physicians acknowledged support from competing companies on one or more drugs they reviewed. Five of those also received such funding from the makers of one or more of the drugs. Yet FDA publicly noted none of those apparent conflicts and issued no conflict waivers.

Science found that AstraZeneca and makers of rival drugs made payments to, or funded research by, several FDA advisers—including Granger—in the year leading up to the 2009 meetings on Seroquel. Granger calls full financial disclosure "crucially important" in order for FDA to assemble the best committee. "I certainly hope that I disclosed everything," he says. "If I hadn't, I would be horrified because that's antithetical to everything I believe in." After initially offering to share his disclosure forms, Granger did not respond to repeated requests for copies. In response to a Freedom of Information Act (FOIA) request, FDA says it could not locate his documents.

Halperin has a similar history. In addition to receiving funds from AstraZeneca and its competitors after he voted to approve the anticlotting drug Brilinta, Halperin was receiving unspecified payments or research support from rival firms during the 12 months before the meeting. He says he disclosed the payments to FDA and that it did not flag them as conflicts. *Science* requested copies of his disclosure materials, but Halperin did not provide them. Again, FDA says it could not locate Halperin's disclosures.

"The system is dependent on the truthfulness of the self-reporting of disclosures," says Genevieve Kanter, a University of Pennsylvania economist who has studied conflicts of interest in FDA drug evaluations. She calls *Science*'s findings of payments to advisers during the year before a committee meeting "significant." And she added that such payments would be "stunning" if consistently large.

The journal disclosures don't specify payment amounts, and the Open Payments data cover only a few years, making such a pattern impossible to show. But an FDA advisory committee that in 2016 voted unanimously to recommend approval of adalimumab-atto (Amjevita), Amgen's immune-altering drug for rheumatoid arthritis, serves as one striking example. Amjevita, which FDA then greenlighted, is similar to AbbVie's

blockbuster adalimumab (Humira), and experts believe Amjevita will be a big seller.

Rheumatologist Daniel Solomon of Harvard Medical School in Boston chaired the Amjevita panel. Neither FDA nor Solomon disclosed publicly that about 3 months before that meeting, Amgen provided $232,000 for his study of etanercept (Enbrel), another arthritis drug made by Amgen, and 1 month before the meeting AbbVie provided $819,000 for a Solomon study of Humira.

That support was for "in-kind donations" of drugs "evaluated as part of a NIH-funded research study for which I am one of the principal investigators," Solomon wrote in an email. He does not regard them as a conflict with Amjevita's approval. Drug donations, a common practice, benefit both parties. Donated drugs help ensure that leading academic specialists will prioritize a company's product in major studies that also enhance the researcher's professional standing and influence. Solomon says he described the payments in an FDA disclosure, but he hadn't kept a copy. The agency rejected a FOIA request for the document, calling its release "a clearly unwarranted invasion of personal privacy."

From such responses, it's not clear whether the agency knew about those potential conflicts and, if so, whether officials decided they didn't warrant a waiver. FDA would not discuss any individual adviser or detail what, if anything, the agency does to validate advisers' disclosures.

Kanter says she favors more research to learn how commonly payments are not disclosed by advisers, or by FDA, to "give us a sense of whether the agency should do some independent verification."

Kessler suggests that greater FDA transparency also could help. "Maybe we need to think about whether the process for reviewing conflicts of interest should be done in a more open, independent manner than the current black box the agency uses," he says. But the former agency head warns that FDA still must find and retain the relatively few specialists "who really can contribute to the issues at hand with exquisite, detailed experience." When so many of them take pharma money, Kessler adds, the agency has to be flexible.

Halperin—one of the 17 top earners and a national leader in cardiology research and practice—puts it bluntly: "The key is disclosure, not squeaky cleanness."

Yet some ethicists say such arguments are unconvincing, if not self-serving. The 107 advisers that *Science* reviewed, combined with 11 federal scientists who served on at least one of the 28 review panels and remain with the government, suggest that potential conflicts can be avoided and often are. Among that group, 47 took less than $800 from pharma after their service on the advisory panel. Thirty-four took no money at all. (Regular federal employees can almost never accept outside compensation.) Elliott argues that the prestige and importance of serving on an FDA advisory committee would outweigh the lure of industry financial favors for many more discipline experts if FDA forced them to choose.

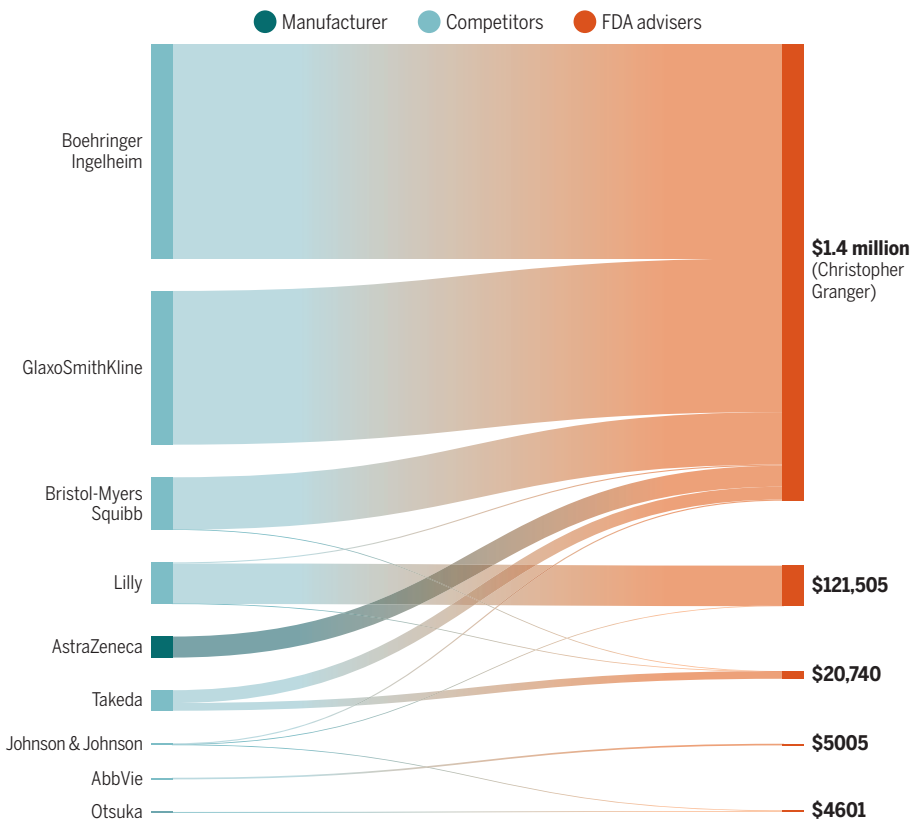
The European Medicines Agency in London, the closest analog to FDA, does force such choices. It has no policy on payments to advisers after serving on a drug advisory panel. However, it bars advisers who have concurrent financial ties to drug companies whose products are under consideration, and it prohibits or strictly limits the participation of advisers whose connections to a company go back at least 3 years before an advisory meeting. Disqualifying factors can include speaking fees, consulting contracts, and research grants—both for scientists conducting industry-sponsored studies and for those, like Halperin, who work on data monitoring committees. The agency investigates financial disclosures on its own initiative or after tips from whistleblowers.

Given the apparent gaps *Science* found, Kanter says the FDA system for evaluating possible conflicts of interest—hidden from the public and based primarily or completely on adviser disclosures—might be strengthened to guard against the clearest causes of potential bias. For example, she found that advisory committee members are more likely to vote for a drug's approval if their financial ties were exclusively to that drug's maker rather than to several companies.

Elliott suggests a more radical solution. "Even in the best of circumstances, disclosure is a remarkably weak way of controlling conflicts of interest," he says. "A better way would simply be for the FDA to say, 'We are not taking anybody with any kind of conflict on an advisory committee.'" ■

After the Seroquel vote

In 2009, FDA advisers voted to recommend approval of the antipsychotic Seroquel for new indications, despite data linking the drug and similar offerings to sudden cardiac death. Four physicians who voted later received funds for consulting, travel, or research from AstraZeneca, Seroquel's maker, and its competitors.



The methodology and data for this story are online at https://scim.ag/FDAanalysis. Meagan Weiland and Katie Langin contributed reporting. The story was supported by the Science *Fund for Investigative Reporting.*

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Is FDA's revolving door open too wide?

By **Charles Piller**

The Food and Drug Administration (FDA) says its rules, along with federal laws, stop employees from improperly cashing in on their government service. But how adequate are those revolving door controls? *Science* has found that much like outside advisers (see main story, p. 16), regular employees at the agency, headquartered in Silver Spring, Maryland, often reap later rewards—jobs or consulting work—from the makers of the drugs they previously regulated.

FDA staffers play a pivotal role in drug approvals, presenting evidence to the agency's advisory panels and influencing or making approval decisions. They are free to move to jobs in pharma, and many do; in a 2016 study in *The BMJ,* researchers examined the job histories of 55 FDA staff who had conducted drug reviews over a 9-year period in the hematology-oncology field. They found that 15 of the 26 employees who left the agency later worked or consulted for the biopharmaceutical industry.

FDA's safeguards are supposed to keep the prospect of industry employment from affecting employees' decisions while at the agency, and to discourage them from exploiting relationships with former colleagues after they depart. For example, former high-level employees can't appear before the agency on the precise issues they regulated—sometimes permanently, in other cases for a year or two.

Through web searches and online services such as LinkedIn, however, *Science* has discovered that 11 of 16 FDA medical examiners who worked on 28 drug approvals and then left the agency for new jobs are now employed by or consult for the companies they recently regulated. This can create at least the appearance of conflicts of interest.

In 2009, for example, an FDA panel weighed whether the agency should approve AstraZeneca's widely prescribed antipsychotic drug quetiapine (Seroquel) for a wider range of conditions. The panel heard from health policy expert Wayne Ray of Vanderbilt University in Nashville, who described his research linking the drug to sudden cardiac death when used with certain other medications. Ray recalls "an FDA staff member who gave a very negative presentation on our paper." That staffer, according to a meeting transcript, was the agency's then-Director of Psychiatric Products Thomas Laughren, who was instrumental in shepherding Seroquel and similar drugs through the review process and personally signed their FDA approvals.

At the meeting, Laughren defended AstraZeneca's clinical trial findings. The company's "analysis should have been able to pick up a difference in sudden cardiac death, and they didn't find any difference between drug and placebo," he said.

Ray told Laughren and the panel that AstraZeneca had pooled data from all its trials as though the data were one data set, causing a well-known statistical error called Simpson's paradox. To take the company's conclusion "as definitive" would be "very

dangerous," Ray said, according to the transcript. Laughren responded by calling sudden death "a pretty definitive event."

Ultimately, the committee voted overwhelmingly to advise approval of the drug for new indications and made no recommendation on labeling it to warn about sudden cardiac death. Later evidence showed that the cardiac problems Ray described are real, and in 2011, FDA required adding a warning on Seroquel's label.

Soon after, Laughren left the agency and formed a consultancy to help psychiatric drug makers, including AstraZeneca, navigate FDA approvals. He did not respond to repeated requests for comment.

In 2012 and 2013, data expert Joan Buenconsejo led FDA's analysis of medical statistics in drug reviews, including offerings from AstraZeneca. In 2014, she joined the company as a director and biometrics team leader. By 2015, Buenconsejo had already represented AstraZeneca before her former FDA colleagues as the company sought a drug's approval. In an email, Buenconsejo wrote that she strictly adhered to FDA's recusal rules "when considering employment with AstraZeneca." She added, "I do not believe there was any conflict of interest around my transition."

Former FDA employees, AstraZeneca spokesperson Karen Birmingham wrote in an email, "bring the perspective of seasoned regulators" who can assist current regulators with the "challenging decisions in approving innovative medicines to meet unmet medical needs."

Jeffrey Siegel, who was an FDA staff member specializing in reviews for arthritis drugs, oversaw the 2010 approval of Genentech's arthritis drug tocilizumab (Actemra). Months later, he left the agency to join the company and its parent, Roche, as director of the division that includes Actemra and related offerings. Siegel represented Roche before his former FDA colleagues when the company sought approval to promote Actemra for new conditions. Last year, he told *STAT* that the timing of his decision to join Roche and Genentech was coincidental.

Laughren, Buenconsejo, and Siegel apparently complied with existing federal laws and FDA requirements. And David Kessler, who led FDA under former Presidents George H. W. Bush and Bill Clinton, says such moves to industry by former FDA experts, steeped in "a culture of drug regulation," can benefit the public if they improve pharma practices. But "revolving door" rules need a fresh look, he adds, to ensure that "the tipping point, where that balance is," serves the public interest.

Vinay Prasad, a hematologist-oncologist at Oregon Health & Science University in Portland who co-wrote the 2016 study in *The BMJ*, contends that weak federal restrictions, plus an expectation of future employment, inevitably bias how FDA staffers conduct drug reviews.

"When your No. 1, major employer after you leave your job is sitting across the table from you, you're not going to be a hard-ass when you regulate. That's just human nature."

ILLUSTRATION: STEPHAN SCHMITZ

Hidden conflicts?

Charles Piller

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