Project On Government Oversight

Drug Problems:
Dangerous Decision-Making at the FDA

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# TABLE OF CONTENTS

Overview ........................................................................................................................................ 3

“FDA Approved” .......................................................................................................................... 4

1. The FDA approved Pradaxa knowing there was no antidote to stop patients on the drug from hemorrhaging. ........................................................................................................ 12

2. The FDA approved the drug on the basis of an unblinded trial that opened the door to potential bias. ................................................................................................................. 14

3. The FDA let the drug company finalize the scoring system after the experiment was over. 16

4. The FDA redacted a key document related to its evaluation of Pradaxa in a way that protected the product’s image at the expense of informing the public. ........................................ 17

5. After refusing to allow the drug maker to claim Pradaxa was superior to warfarin, the FDA acceded to the company’s wishes and permitted it to make the stronger marketing claim... 19

6. For years, the FDA allowed Boehringer Ingelheim to make another marketing claim about the drug that the FDA itself eventually concluded was “misleading.” ............................ 20

7. The FDA tolerated sloppiness and arguably loose controls in the management of the clinical trial................................................................................................................................. 21

   Initial application rejected......................................................................................................... 21

   Sloppy Science: Inspections document regulatory violations in RE-LY trial ....................... 22

8. When doctors helping to oversee the trial were found to have mismanaged their part of it, the FDA’s response appeared toothless. ............................................................................ 23

9. Doctors faulted by the FDA in earlier trials participated in the testing of Pradaxa. ............ 27

10. The publicly available records of FDA inspection results are less than transparent, shielding clinical trials from public scrutiny and accountability. .................................................... 31

11. When adverse event reports naming Pradaxa mounted, fueling concern about the blood thinner, the FDA issued statements defending the new drug. But outside experts say the analysis behind those statements was glaringly flawed. ......................................................... 31

12. Though Pradaxa can cause fatal bleeding, and though there is no antidote, the FDA has not required the drug to carry a conspicuous “black box” warning about those hazards like the warning applied to warfarin. .............................................................. 34

13. Members of the FDA advisory committee that unanimously endorsed Pradaxa had extensive ties to the pharmaceutical industry. Two went on to receive substantial compensation from the maker of Pradaxa. .......................................................... 36
14. Former FDA advisory committee members helped Boehringer Ingelheim prepare for its appearance before the FDA’s Cardiovascular and Renal Drugs Advisory Committee, further blurring lines between the regulatory system and the interests it regulates. .......................... 39

15. The FDA approved Pradaxa without a system to test patients’ blood and tailor dosing. ..... 42

Epilogue: Years after approving Pradaxa, the FDA appears to be having some second thoughts about its approach to the drug................................................................. 46

Recommendations................................................................................................... 48

Endnotes .................................................................................................................. 50

Credits ..................................................................................................................... 79
On July 14, 2011, a retired social worker named Sidney Denham was taken to an emergency room in Savannah, Georgia. Weeks after undergoing prostate surgery, and days after resuming use of a relatively new blood thinner called Pradaxa, the 81-year-old widower was bleeding profusely from his urinary tract. He had lost so much blood that his pressure had plunged to about half the normal level and his body was in shock. In the intensive care unit, a medical team deployed treatment after treatment in a struggle to save him.¹

One of Denham’s daughters, Kay Denham, recalled the scene: “More blood than I think I’ve ever seen in my life . . . Millions of people in the room . . . They could not control the bleeding.”²

A hospital record shows that Denham was given 12 units of red blood cells and another 12 of fresh-frozen plasma—almost two gallons. He was pumped with platelets and other blood products. He was put on dialysis to purge the Pradaxa from his system. Nothing worked.

Even as they replaced his blood, it was draining out of him.³

“It was horrible,” said daughter Mary Denham, “that feeling of helplessness, for the people in the ER and for us. There was nothing they could do to stop the bleeding. My sister and I watched him bleed to death.”⁴

Denham had been taking the anticoagulant Pradaxa to treat a condition called atrial fibrillation, in which irregular functioning of the heart can cause blood clots and strokes; the medicine is supposed to prevent the clots from forming.⁵ But, according to Denham’s “DEATH SUMMARY” from Memorial University Medical Center in Savannah, the FDA-approved drug contributed to his demise.

The patient, the document says, suffered an “uncontrollable hemorrhage from Pradaxa.”⁶

Overview

The Food and Drug Administration is responsible for making sure medicines sold to the public are safe and effective.⁷ But how much comfort should medical consumers take from the words “FDA approved”?⁸

In judgment call after judgment call involving the prescription blood thinner Pradaxa, which has been named as a suspect in thousands of patient deaths, the FDA took a lax or permissive approach, a Project On Government Oversight investigation has found.⁹

The result was to accommodate a pharmaceutical company by easing a drug’s passage to market and then deflecting questions about its safety once the product had won approval. The issues ranged from what standards to demand from the manufacturer-sponsored clinical trial used to secure the drug’s approval to what warnings to give patients about potential hazards and what claims to allow in ads for the product.

POGO’s findings, based on interviews with key participants and researchers and upon thousands of pages of public records, many obtained through the Freedom of Information Act, call into question the reliability of a crucial regulatory system.
“FDA Approved”

For protection from the potentially distorting effects of drug makers’ profit motive, and for sound scientific judgments, the public depends on regulators. But, time and again, far from resolving questions about a drug’s safety or effectiveness, FDA approval has become a prelude to pharmaceutical scandal or controversy. The history stretches from Vioxx and Avandia to Yaz and Yasmin, from Fen-Phen to Baycol, Darvon, Ketek, and Paxil. In some cases, drugs approved by the FDA after undergoing supposedly rigorous clinical trials have gone on to cause serious harm. In other cases, after drugs have been allowed on the market, questions set in. Doctors, patients, and FDA regulators alike have been left struggling to determine whether serious or deadly mishaps are actually side effects—whether drugs meant to help people are actually hurting them. Were significant risks foreseen before the drugs were approved, or were they foreseeable? Were they properly weighed and disclosed? Did the clinical trials used to test the drugs provide a sound basis for FDA approval? Once the drugs were released to the market, how did the FDA track and respond to whatever happened next? Fundamentally, how well did the agency do its job?

To shed light on the FDA’s oversight of prescription drugs, POGO took a close look at one drug’s journey from clinical trial to regulatory approval and beyond. From the drug’s origins in a pharmaceutical company’s research laboratories, the steps in the process included a clinical trial in which the company and doctors working on its behalf tested the drug in thousands of human guinea pigs around the world; inspections in which the FDA scrutinized the performance of a sample of those doctors; analysis of the clinical trial’s results by FDA staff; a hearing and vote by an advisory committee of outside experts convened by the FDA (though advisory committee recommendations are non-binding, the FDA generally follows them); the FDA’s decision to approve the drug; and, once the drug was cleared for use in the United States, ongoing FDA oversight of such issues as the drug maker’s marketing activities and the occurrence of side effects in people taking the drug.

POGO chose to focus on Pradaxa—also known by the generic name dabigatran—because, after it was approved by the FDA in 2010, it became one of the drugs most frequently named in so-called “adverse event” reports submitted to the agency about suspected side effects. In 2011 and 2012, Pradaxa was the drug most frequently named in adverse event reports submitted directly to the FDA by doctors, patients, family members and the like, according to reports by the Institute for Safe Medication Practices (ISMP), which tracks data on adverse events. By September 2012, it had been identified as the primary suspect in almost 2,000 reports about patient deaths, according to data from another source, adverseevents.com.

Such reports do not prove that a drug caused a medical mishap like Sidney Denham’s fatal hemorrhage, but they identify it as a potential factor. Pradaxa was associated with hemorrhages.

The adverse event reports were not the only causes for concern. In 2012, the drug’s manufacturer, Boehringer Ingelheim, prematurely stopped a follow-on clinical trial of Pradaxa use in patients with mechanical heart valves because subjects taking the drug were suffering from excessive blood clots and bleeding.

The FDA approved Pradaxa in 2010 for prevention of strokes and blood clots in patients with atrial fibrillation, a condition estimated to affect 2.7 to 6.1 million people in the United States.
It was the first of a new type of anticoagulant and, the manufacturer says, the first oral anticoagulant approved by the FDA for non-valvular atrial fibrillation in more than 50 years. It has been sold to the public as offering a distinct advantage over warfarin, the decades-old drug it was meant to replace: patients taking it wouldn’t need to undergo regular blood tests.

Other new anticoagulants in Pradaxa’s class include Eliquis (generic name apixaban), Savaysa (edoxaban), and Xarelto (rivaroxaban), which is promoted in television ads featuring golfer Arnold Palmer, NASCAR driver Brian Vickers, and comedian Kevin Nealon.

Pradaxa “posted mammoth results in 2012, reaching blockbuster status in its second full year, with $1.4 billion in sales,” an industry publication reported. As of November 3, 2014, it had been prescribed for more than 935,000 patients in the United States, according to the manufacturer.

Meanwhile, Boehringer Ingelheim became the target of thousands of lawsuits filed by Pradaxa patients and their families, including the Denhams.

While the litigation was playing out, the federal judge presiding over it, Chief Judge David R. Herndon of the U.S. District Court for the Southern District of Illinois, found that the company had been withholding or failing to preserve records sought by plaintiffs. He fined Boehringer Ingelheim $931,500 and accused the company of acting in “bad faith.”

Some of the documents cited in the judge’s December 2013 order—internal company emails—appear to raise questions about one of the drug’s principal claimed advantages, the notion that there is no need to monitor patients’ blood and adjust their doses in response. According to the judge’s order, a high-level scientist at Boehringer Ingelheim named Thorsten Lehr drafted a paper concluding that, as the judge paraphrased it, “both safety and efficacy of dabigatran are related to plasma concentrations and … there is a therapeutic range for Pradaxa.” (The term “therapeutic range” means a range within which a drug is typically expected to yield the desired results.)

The judge recounted that others inside the company resisted publishing that conclusion.

“I have been facing heavy resistance internally on this paper about the concept of a therapeutic range, at least stating it outright,” Paul Reilly of Boehringer Ingelheim, who was tasked with revising the paper, said in an internal email quoted by the judge.

Publishing the information “will make any defense of no monitoring … extremely difficult … and undermine our efforts to compete” with other new anticoagulants, Boehringer Ingelheim’s Jutta Heinrich-Nols said in a February 2013 email that was posted online by The New York Times.

In May 2014, against the backdrop of those disclosures, Boehringer Ingelheim agreed to settle Pradaxa litigation for $650 million. The company said it was trying to put about 4,000 claims involving the drug behind it, and it conceded no liability. “We continue to stand resolutely behind Pradaxa® and believed from the outset that the plaintiffs’ claims lacked any merit,” Andreas Neumann, the company’s general counsel, said in a news release at the time.
To be sure, there might have been legitimate arguments on both sides of health and safety issues confronted by regulators. However, taken together, the FDA’s decisions about Pradaxa add up to a troubling pattern. For example:

- The FDA approved Pradaxa despite the absence of an antidote to thicken the blood and stop patients from bleeding uncontrollably if they start to hemorrhage. Unlike warfarin—the longtime standard for blood-thinning—Pradaxa has no reversal agent.

- As reports of fatal hemorrhages in patients taking Pradaxa fueled concern about the safety of the blood thinner, the FDA issued statements defending the new drug. But outside experts said the scientific analysis behind those statements was deeply flawed and that the FDA should not have reassured the public on the basis of it. Jerry Avorn, a professor at Harvard Medical School, wrote that the FDA’s analysis ignored key variables and was “unsuitable for informing the care of patients.” David Madigan, professor of statistics and dean of the Faculty of Arts and Sciences at Columbia University, called the FDA’s Pradaxa study “junk.”

- Though Pradaxa can cause fatal bleeding, and though there is no antidote—dangers acknowledged in the fine print of the product’s package insert—the FDA has not required the drug to carry a more conspicuous “black box” warning about those hazards. (In contrast, the decades-old warfarin carries a warning framed in a black box about “major or fatal bleeding.”)

- The FDA approved the drug on the basis of an unblinded trial. Researchers knew which subjects were taking the experimental drug, and, according to a key FDA reviewer, handled them differently.

When patients in the study showed signs of trouble, those on Pradaxa were more likely to have their treatment discontinued, an FDA review found. As a result, adverse events such as hemorrhagic strokes that might have occurred had they continued taking Pradaxa would have been averted, cardiologist Steven Nissen, who served on an FDA advisory committee, explained. That would make Pradaxa look safer than it was. Addressing the committee, Nissen said the possibility the trial was biased was “the elephant in the room.”

At the same meeting, Aliza Thompson, a medical officer in the FDA’s Division of Cardiovascular and Renal Products, voiced concern that the unblinded approach “sort of inflates the findings relative to warfarin.”

FDA records show that the agency expressed a preference for a double-blind study (in which the people on the clinical trial’s front lines would not know which patients were taking which drug)—but did not insist upon it.

- The FDA approved the drug on the basis of a single clinical trial. The absence of another trial confirming the results of the first “adds a measure of uncertainty,” Thompson told the advisory committee.
The scoring system for the clinical trial was not finalized until the trial was over. A key document called the Trial Statistical Analysis Plan specified, among other things, criteria for determining whether adverse events such as strokes and heart attacks were to be counted as part of the study’s results or left out. But the Statistical Analysis Plan was not finalized until May 8, 2009, about two months after the data had been gathered and the study had ended, according to FDA documents.40

An FDA review found that the way the lines were drawn helped Pradaxa in comparison to warfarin with respect to mortality rates.41

In its publicly posted memo announcing and explaining its decision to approve Pradaxa, the FDA redacted its assessment of the drug in a way that protected the product’s image at the expense of informing the public.42 The deleted section, which POGO obtained through the Freedom of Information Act (FOIA), said that patients who were well-treated using warfarin had no reason to switch to Pradaxa.43

Initially, the FDA refused to allow Boehringer Ingelheim to claim Pradaxa was superior to warfarin. The agency concluded that the experimental data did not warrant such a claim. But, without much of an explanation for its change of heart, the FDA later acceded to the manufacturer’s request and allowed the company to make a superiority claim.44

The FDA allowed Boehringer Ingelheim to make another promotional claim that the agency itself eventually declared “misleading.” The manufacturer originally advertised that, in a clinical trial, Pradaxa “reduced stroke risk 35% more than warfarin.”45 After the drug had been on the market for more than two and a half years, the FDA explained that it had changed its opinion about the 35 percent claim and it directed the company to add a clarification: “That means that in a large clinical study, 3.4% of patients taking warfarin had a stroke compared to 2.2% of patients taking Pradaxa.” In other words, in absolute terms, the difference between the drugs was only 1.2 percent.46

The FDA tolerated sloppiness and arguably loose controls on the part of the drug maker in its management of the clinical trial. The agency’s own inspection documented regulatory violations by Boehringer Ingelheim, according to an FDA memo. The inspection found such violations as “failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan.”47

When the company originally submitted its application for approval of Pradaxa, the agency refused to even consider it because it was riddled with errors and numbers the FDA described as “highly implausible.”48

When doctors helping to run the trial were found by FDA inspections to have mismanaged their part of it, the FDA did not restrict their participation in future clinical trials. As far as POGO could determine from public records, at most, the FDA gave them a warning or reprimand and asked them to explain how they would avoid repeating their mistakes. According to FDA documents, those mistakes included enrolling patients with liver disease and severe kidney impairment even though such patients were supposed to
be excluded from the study, failing to promptly inform the drug maker about possible adverse effects of the experimental drug, failing to obtain the fully informed consent of human research subjects, and failing to oversee the study closely enough “to protect the rights, safety, and welfare of subjects enrolled in the study.”

• The FDA’s handling of offenders in the Pradaxa trial appeared to be par for the course. Based on a review of FDA records and other documents related to the clinical trial, dozens of researchers the FDA had cited in the past for violating the standards for clinical trials, including repeat or even three-peat offenders, were allowed to enroll and monitor patients in the Pradaxa trial.

• Looking beyond the Pradaxa trial, a POGO analysis of 10 years of FDA inspection data shows how infrequently the FDA has inspected “clinical investigators”—medical professionals treating and tracking human subjects in clinical studies—and how rarely the FDA has imposed sanctions on doctors whose performance the agency faults. From 2005 through 2014, in trials of new experimental drugs, the FDA found deficiencies in the work of about 50 percent of the clinical investigators it inspected—1,573 of 3,120. More than 170 of those investigators received an inspection code at the severe end of the scale, indicating that their violations were “significant/serious and/or numerous.” Over that same period, in the realm of drug evaluation, the FDA disqualified only 26 clinical investigators from participating in clinical trials.

(To put those numbers in some perspective, there were more than 1,500 clinical investigators in the Pradaxa trial alone, and, from 2005 through 2014, there were more than 170,000 clinical trials of various kinds registered with the National Institutes of Health site ClinicalTrials.gov.)

• Members of the FDA advisory committee that reviewed Pradaxa and endorsed it by a vote of nine to zero had ties to the pharmaceutical industry. Financial disclosures for later years show that two of those committee members developed substantial financial relationships with Boehringer Ingelheim. According to his curriculum vitae, in 2013, one of them became “Study Co-Chair” of a clinical trial that is identified elsewhere as sponsored by Boehringer Ingelheim. A public database that goes back to 2012 shows that, over a recent three-year period, he received payments from the maker of Pradaxa totaling between $75,000 and $134,994. The other former committee member went on to receive payments totaling $95,764 from Boehringer Ingelheim, according to a different database that covers only 2013 and 2014.

• Further blurring the lines between the regulatory system and the interests it regulates, when Boehringer Ingelheim held a practice session to prepare for its questioning by the FDA advisory committee, a former member and a former chairman of that committee were paid to play roles in the rehearsal. Members of the advisory committee that reviewed Pradaxa later took on roles at a consulting firm that specializes in helping drug companies win the support of FDA advisory committees.
In addition to approving the drug in the absence of an antidote, the FDA approved the drug in the absence of a system to monitor patients’ coagulation levels and adjust dosing—burdensome requirements associated with taking warfarin.

On this issue, as on others, the FDA and its advisors took an eyes wide shut approach—spotting the issue but looking past it nonetheless. As one advisory committee member who voted to approve Pradaxa recently told POGO, “I didn’t understand how anybody could take a drug that thins the blood and not check it.”

The chance to do without regular blood tests was touted as a key Pradaxa advantage when the manufacturer made its pitch to the FDA and, later, when the company advertised the drug to consumers. But the information that came to light in litigation against Boehringer Ingelheim—about research that company insiders resisted publishing—suggests that at least some testing might have had value for some Pradaxa patients. In hindsight, it makes the FDA’s handling of Pradaxa appear even more questionable.

In a May 2012 email quoted by the judge, Boehringer Ingelheim Corporate Senior Vice President of Medicine Klaus Dugi hypothesized that monitoring could lead to “a reduction of major bleeding events compared to well-controlled warfarin of perhaps up to 30-40%.”

A senior FDA official has argued more recently that “optimizing dose or blood level seems like a very good idea.”

Years after Pradaxa won FDA approval, Boehringer Ingelheim submitted for FDA approval a drug to reverse Pradaxa’s blood-thinning effect—acknowledging, in effect, that having an antidote available would be a good idea. The FDA thought the experimental antidote was so important that it decided to review it on an expedited basis. That review is pending.

How Pradaxa measures up in terms of safety and efficacy have been subjects of scientific debate, and this report does not take sides in that debate. What POGO’s investigation shows is, in the FDA’s oversight of Pradaxa and in the factors it was willing to overlook when reviewing the manufacturer’s clinical trial, the agency has appeared permissive. It is unclear why the agency was so willing to accommodate the drug maker. The FDA’s own record appears to contain good reasons for the agency to have taken a different approach.

“The FDA actions since dabigatran was approved in 2010 have been almost entirely supportive of dabigatran and apparently intended to discount safety concerns,” the Institute for Safe Medication Practices said in an October 2013 report, referring to the drug by its generic name.

BMJ, formerly known as the British Medical Journal, put it this way: “[R]ecent insights into the development and approval of dabigatran—the first new oral anticoagulant brought to market—have raised serious questions about its risks. … In effect, the current situation leaves clinicians and patients the choice between the devil they know and the one they don’t.”
In a 2014 news release responding to coverage in *BMJ*, Boehringer Ingelheim defended its product and the study that served as the basis for FDA approval, the clinical trial conducted by Boehringer Ingelheim and known as “RE-LY.”

“RE-LY® showed Pradaxa® to be a breakthrough for improving stroke prevention versus standard of care,” the company said.

“The design of the RE-LY® trial, which studied two different doses of Pradaxa® in one trial, was intensively discussed and agreed with regulatory authorities as it was found to be robust and valid,” the company added.  

Asked about flaws in the RE-LY trial, the FDA’s Gerald J. Dal Pan said:

“There are many things found to be wrong—our job is to poke holes in trials. We go looking under every rock. If you look at our reviews on any drug trial, you’ll find that when we looked under all the rocks we find all kinds of gremlins and goblins and sites where they didn’t do things quite right, and people who didn’t take the drug quite right. That happens. But we have to apply judgment and look at all that in the context of what’d ya got?”

The agency’s Ellis Unger struck a similar note.

“I’m inherently skeptical of every company,” he said. “[T]hey tell you that they care about patients, but we know what companies are here for. So we look at everything as carefully as we can.”

In a presentation to the FDA advisory committee, a leader of the Pradaxa clinical trial highlighted the heart of the case for Pradaxa. Salim Yusuf said that higher risks of gastrointestinal hemorrhage and heart attack for patients taking Pradaxa came with a benefit: reduced risk of bleeding in the brain. Yusuf called intracranial hemorrhages “the most dreaded fear” associated with warfarin and “a devastating complication.”

Boehringer Ingelheim provided some information to POGO and answered some questions early in POGO’s work on this report. Then, in the fall of 2013, the company declined to respond further.

“Consistent with our prior communications, we will not provide further response beyond what we previously provided and beyond the wide range of information we have released to the public regarding the favorable benefit-risk profile of Pradaxa,” company spokeswoman Lauren Murphy said in an August 2015 email.

Asked to highlight any information released to the public that Boehringer Ingelheim regarded as responsive to POGO’s questions, Murphy replied, “I would direct you to our website: http://us.boehringer-inglesheim.com/news_events/press_releases.html.”

Questions about FDA oversight aren’t limited to Pradaxa, even within the realm of blood thinners. In its handling of two of the other new anticoagulants, the FDA acted over strong objections from within the agency, taking a similarly permissive or forgiving posture toward the drugs, the manufacturers, and the clinical trials.
In the case of Xarelto, also known as rivaroxaban, the primary clinical reviewers evaluating the drug recommended that the FDA not approve it, according to a memo laying out the agency’s decision to approve it nonetheless.\(^7^6\)

“[I]f rivaroxaban is approved, patients taking it might be at greater risk of harm from stroke and/or bleeding than if they were treated with warfarin used skillfully,” the reviewers had written.\(^7^7\) They argued that warfarin use was not controlled well enough in the clinical trial of Xarelto, and that as a result the trial might have been biased in favor of Xarelto.\(^7^8\) They also believed that Xarelto should be administered twice a day—not once, as tested by the manufacturer.\(^7^9\) Even some FDA advisory committee members who voted in favor of Xarelto’s approval were concerned about the one-a-day dosing “being used as a marketing ploy,” the advisory board minutes said.\(^8^0\)

In a memo explaining why the FDA dismissed those objections, Deputy Division Director Stephen M. Grant said Xarelto was tested in “a ‘real world’ trial,” and he seemed to embrace a less-than-assertive interpretation of the FDA’s authority.

He said there was no evidence that the maker of Xarelto deliberately chose investigators who were unskilled at managing warfarin doses.\(^8^1\)

Grant sympathized with the reviewers’ concern about Xarelto’s dosing, saying that, given the drug’s half-life of less than 12 hours, taking only one pill per day could lead to a sharp drop between doses in the level of Xarelto in the patient’s system. He wrote that, in designing the clinical trial, the manufacturer had rejected the FDA’s advice to test two doses per day. But the FDA didn’t let that stand in the way of the drug’s approval. “Absent significant toxicity,” Grant wrote, “inadequate dose exploration is rarely an impediment to approval.”\(^8^2\)

A spokeswoman for Janssen, the maker of Xarelto, said in an email that the Xarelto clinical trial “demonstrated the safety and efficacy of once-daily” dosing. The FDA approved the drug “based on the positive benefit-risk profile” observed in the study, she added.\(^8^3\)

In the case of Eliquis, an FDA official argued against the agency’s conclusion that, compared to warfarin, the drug reduces deaths, according to a recent news report. The Milwaukee Journal Sentinel and MedPage Today jointly reported that the official, Thomas Marciniak, argued that missing data on hundreds of patients rendered the Eliquis clinical trial inconclusive on that point.\(^8^4\)

In a 2012 memo the two publications posted online, Marciniak said the problem was part of a broader pattern.

“I consider it to be very unfortunate that [the Eliquis trial], like many other recent outcome trials, has substantial problems with data quality,” Marciniak wrote. “Some of the responsibility for the data quality problems rests with us, the FDA: We have approved drugs ignoring similar data quality issues, granting superiority claims and not discussing in the labels the data quality issues. We must stop doing this.”\(^8^5\)

Other FDA reviewers wrote that the volume of missing data in the Eliquis trial was “not especially large,” adding that it was unclear which way, if at all, the missing data tilted.\(^8^6\) A spokesman for Pfizer, one of the marketers of the drug, said: “As the FDA ultimately decided,
the small fraction of patients lost to follow-up did not adversely alter the interpretation of superior results vs. warfarin.”

Like Pradaxa, the other new blood thinners were approved by the FDA without antidotes.

POGO’s glimpse inside the FDA serves as a cautionary tale as Congress advances a bill called the 21st Century Cures Act. Passed by the House in July with strong support from both parties, the bill has been touted as a way to speed needed cures to patients. In fact, it could open the door to a dramatic lowering of standards for FDA approval, allowing drug companies and other manufacturers to market unproven products. Diana M. Zuckerman, president of the National Center for Health Research, has written that it would turn patients “into unwitting guinea pigs while making them pay for the privilege.”

The process that led to Pradaxa’s approval and the record of FDA oversight since then do not inspire confidence in the regulation of prescription drugs. They do, however, suggest ways that the system could be improved. Those include a greater emphasis on safety and an insistence on higher standards in the clinical trials on which the system depends.

1. The FDA approved Pradaxa knowing there was no antidote to stop patients on the drug from hemorrhaging.

Perhaps the most basic accommodation the FDA made for Pradaxa was approving it with the knowledge that it could lead to uncontrollable hemorrhages.

Thinning the blood is inherently dangerous; thinning it too much can cause bleeding. That is true not just of Pradaxa but also of any anticoagulant, including the old standard known generically as warfarin and by the brand names Coumadin and Jantoven. The dangers range from a little loss of blood to death. The bleeding can occur spontaneously—say, from the gastrointestinal tract—or it can be brought on by an accident or injury, making familiar medical emergencies harder to manage.

But, unlike warfarin, which has been on the market for six decades, Pradaxa has no antidote—no ready agent to reverse the anticoagulation process and stop the bleeding. In contrast, warfarin can generally be reversed with a shot of Vitamin K or a cocktail of clotting factors.

“In contrast to warfarin, effective interventions to stop dabigatran-related hemorrhage have not been established,” a 2010 report by FDA staff said.

The absence of an antidote raised the stakes in the FDA’s review of Pradaxa, heightening the potential cost of misjudgment on other points.

The FDA apparently concluded that the benefits it saw in Pradaxa justified the risk. Pradaxa had the potential to improve life for patients with atrial fibrillation by freeing them from dietary restrictions associated with warfarin. In addition, billed as working without dose adjustments, it promised to free them from the need for periodic blood tests to determine whether their clotting is within the appropriate range.
If new, easier-to-use anticoagulants could prompt greater numbers of patients with atrial fibrillation to take blood thinners, more patients could be protected from the dangers of the condition, FDA officials have reasoned.\textsuperscript{97}

Responding to concerns about Pradaxa, FDA officials have also argued that it is more effective than warfarin at reducing strokes, and that the potentially devastating consequences of strokes outweigh other considerations.\textsuperscript{98}

However, before Pradaxa was approved, and in a memo explaining the agency’s decision to approve Pradaxa, FDA staff essentially recommended that statistics purporting to show Pradaxa’s advantages be taken with a large grain of salt.\textsuperscript{99}

If the absence of an antidote for Pradaxa gave anyone at the FDA serious pause, that concern was not apparent when an FDA advisory committee held a hearing on Pradaxa. While the advisory committee listened to presentations by FDA staff and representatives of the drug company, asked questions, and debated various issues, there was no discussion of the fact that the experimental drug came with no reversal agent.\textsuperscript{100} Nor was it mentioned in the “Decisional Memo” an FDA official wrote reviewing the risks and benefits of the drug and explaining his decision to approve it.\textsuperscript{101}

“It was obvious going in that there was no specific antidote,” advisory committee member Sanjay Kaul recalled. “So it was not surprising it did not come up for discussion.”\textsuperscript{102}

 Nonetheless, even some advisory committee members who endorsed Pradaxa’s approval remained reluctant to prescribe it to their own patients. Almost five years later, cardiologist Steven Nissen of the Cleveland Clinic said he had yet to put a single patient on the drug.\textsuperscript{103} “I prefer warfarin for its low cost and ease of reversal in case of bleeding,” Nissen has told POGO.\textsuperscript{104}

Asked some time ago how he treated Pradaxa patients who showed up at his hospital with a hemorrhage, Nissen gave POGO a succinct answer that was only partly in jest:

“Pray,” he said.

“Transfuse and pray,” he said later.\textsuperscript{105}

In product liability litigation over Pradaxa, a Boehringer Ingelheim employee testified that, even with an antidote, it can take time to reverse the effects of warfarin. “[I]t can take hours, even days, until the anticoagulatory effect could be reversed through vitamin K. And during this time, bleeding could also continue,” Boehringer Ingelheim senior medical advisor Martina Brückmann said in a deposition.\textsuperscript{106}

If that reasoning pointed to the need for an alternative with a faster antidote, neither the FDA nor Boehringer Ingelheim waited for one.

In September 2013, about three years after the FDA approved Pradaxa, and after the drug had been named in thousands of reports about patient deaths, Boehringer Ingelheim began a clinical trial of an experimental antidote.\textsuperscript{107} The reversal agent, which would be the first for any of the new oral anticoagulants, is now awaiting FDA action.\textsuperscript{108}
“We all agree it would be better to have a reversal agent” for Pradaxa, Robert Temple, the FDA’s deputy director for clinical science, said in a 2013 interview with POGO. “Nobody doubts that.”

2. The FDA approved the drug on the basis of an unblinded trial that opened the door to potential bias.

Ideally, clinical trials are conducted on a “double-blind” basis, meaning that neither the subjects of the study nor the people administering it know who is receiving the experimental treatment. That approach—a basic, standard precaution in clinical research—is meant to prevent bias from creeping in and skewing the results, either consciously or otherwise.

But, researchers in the Pradaxa study knew which subjects were taking the experimental drug, and, according to one of the main FDA reviewers, handled them differently.

When patients in the study showed signs of trouble, those on Pradaxa were more likely to have their treatment discontinued, an FDA review found. As a result, adverse events such as major hemorrhages that could have occurred had they continued taking Pradaxa would have been averted, advisory committee member Steven Nissen explained. In other words, the clinical trial results might have understated the risks of using Pradaxa. (Nissen gave the illustration of a patient on Pradaxa experiencing bleeding while brushing his or her teeth, being taken off the drug in response, and thereby avoiding a stroke.)

FDA records show that the agency wanted Boehringer Ingelheim to test Pradaxa on a double-blind basis. However, the manufacturer took a different approach, and the FDA went along with it. Ultimately, the agency approved Pradaxa despite the determination that lack of blinding might have affected the data.

Before the FDA approved two other new generation anticoagulants, Eliquis and Xarelto, those were compared to warfarin in double-blind clinical trials.

When the FDA considered whether to approve Pradaxa in 2010, it did so on the basis of a single clinical trial that compared Pradaxa’s safety and effectiveness to that of warfarin in about 18,000 atrial fibrillation patients around the world over a period of about three and a half years. Some were given the experimental drug and the rest were given the established, decades-old drug. The trial, known as RE-LY, was sponsored by the drug’s manufacturer, as such trials ordinarily are.

In the RE-LY trial, both patients and people administering the study knew who was on warfarin, and those patients underwent the regular blood tests associated with warfarin. In contrast, the two doses of Pradaxa tested in the clinical trial were administered on a blinded basis—meaning it was not apparent who was taking the 150 mg dose and who was taking the 110 mg dose—reflecting the importance generally attached to that approach.

The review package the FDA staff prepared describes the position the agency took with the drug maker in 2005, before the RE-LY trial began. A summary of “Advice from Agency” includes these points: “double-blind trial preferred; more detail regarding why blinding was not feasible should be provided” and “concern raised for ascertainment bias … given open-label nature of study.”
Jonathan C. Fox of drug-maker AstraZeneca, who was the non-voting industry representative on the FDA’s Cardiovascular and Renal Drugs Advisory Committee, alluded to this history when the advisory committee met. “You know, the agency, I think, made it very clear to the sponsor at the outset and along the way that they preferred a double-blind design,” Fox said. “The sponsor chose to conduct the trial a bit differently . . . It doesn’t seem that they were punished in any way upon filing and review.”

The FDA medical officer responsible for reviewing Pradaxa’s effectiveness said that the lack of blinding skewed the study.

One of the “key messages,” FDA reviewer Aliza Thompson told the advisory committee, was that “knowledge of treatment assignment in RE-LY clearly affected how the patients were treated." Thompson, clinical team leader in the FDA’s Division of Cardiovascular and Renal Products, spoke of possible bias in the trial and concern that the unblinded approach “sort of inflates the findings relative to warfarin.”

Nissen, a cardiologist at the Cleveland Clinic, said the possibility the trial was biased was “the elephant in the room.”

“You know, clinicians are pretty smart, and there may have been harbinger events, maybe minor bleeding, other things, that caused them to discontinue the drug, that had it continued the patient would have had a serious major bleed,” Nissen told his colleagues on the advisory committee. Pradaxa’s perceived advantage in the trial in the prevention of hemorrhagic stroke “may in fact be an artifact of the differential discontinuation, to some extent,” he said.

Nissen stressed the importance of blinding:

“There is a reason why we do double-blind studies. If you could eliminate all bias in open-label studies, then we’d just do open-label studies. They are a whole lot easier to do. So you have to assume that no matter how good the intentions are of the people involved, and I do think that there was a lot of effort put in to try to do a good open-label trial, it is still an open-label trial. And an open-label trial, by definition, has inherent biases. So the issue that we’ll have to think through here is how much . . . But you can’t be entirely comfortable with any open-label trial involving a drug of this importance, that’s going to be taken by this number of people, given the fact that there may be biases we can’t even measure or understand in trials.”

Even a member of the Boehringer Ingelheim team seemed to acknowledge that bias was a factor in the RE-LY trial. In a presentation to the advisory committee, Paul Reilly suggested the higher discontinuation rate for patients on Pradaxa (dabigatran) reflected conscious choices: “It does appear that the investigators—that the investigators or the patients were not very comfortable with adverse or other new events occurring in a new chemical entity and were more likely to discontinue therapy despite the fact that the events occurred with less frequency on dabigatran.”

Had the trial been blinded for Pradaxa vs. warfarin, patients on Pradaxa would have had to undergo dummy monitoring tests. That would have eliminated from the comparison one of Pradaxa’s theoretical advantages: the notion that patients taking the experimental drug did not have to have their blood tested, making it an easier drug to use and presumably giving patients one less reason to stop using it or to fall out of compliance with the regimen.
As a warning that unblinded trials may be unreliable, FDA reviewers noted that another blood thinner was tested on both a blinded and an unblinded basis. An open-label study found that that drug was as good as warfarin, but a blinded study did not. When researchers knew which patients were taking the experimental drug, they recorded fewer strokes and blood clots for patients on the experimental drug.

(One might think it would be clear whether patients in the Pradaxa clinical trial suffered serious adverse events such as strokes or systemic embolisms—the type of outcomes the trial was meant to measure—but determining whether patients actually suffered such events turned out to be somewhat subjective. Stuart Connolly, a leader of the trial, told the advisory committee that different groups of RE-LY adjudicators agreed 85 or 86 percent of the time on strokes and 85 to 90 percent of the time on major bleeds and other events but only 50 percent of the time on “non-CNS systemic embolism,” apparently referring to blood clots that do not involve the central nervous system.)

For Thompson and some members of the FDA advisory committee, the lack of blinding in the RE-LY trial was a reason to deny Boehringer Ingelheim the ability to claim Pradaxa was superior to warfarin—but not grounds to reject the drug altogether. The drug could still be approved as “non-inferior,” meaning it was no worse than warfarin.

Overcoming his concern about “the elephant in the room,” Nissen reached the same conclusion.

“I voted yes [to approve the drug] for a couple reasons, and one is that no matter how I penalize the trial for the open-label design you can’t make this non-inferiority go away,” he said.

Following the advisory committee’s unanimous recommendation, the FDA initially approved Pradaxa as non-inferior. But, as discussed below, it later relented and granted the superiority claim the company sought.

And, as discussed elsewhere in this report, a key premise for conducting an open-label study—the notion that Pradaxa patients need not be monitored with blood tests—has since been called into question by documents that surfaced in litigation against the manufacturer.

3. The FDA let the drug company finalize the scoring system after the experiment was over.

A key document called the Trial Statistical Analysis Plan specified, among other things, criteria for determining whether adverse events such as strokes and heart attacks were to be counted as part of the study’s results or left out. In the RE-LY trial, the Statistical Analysis Plan was not finalized until May 8, 2009, about two months after the study’s end date, according to the FDA review package.

The FDA review indicated that the way the lines were drawn benefitted Pradaxa in comparison to warfarin with respect to mortality rates. (For a more detailed technical discussion, see endnote 139.) FDA reviewer Aliza Thompson raised the same issue before the advisory committee.

Two general points seem clear: The FDA was troubled that the rules of the trial were finalized so late in the process, and the agency’s concern was more than academic.
An FDA document shows that the agency was disturbed about efforts to revise the Statistical Analysis Plan as early as 2008 and conveyed its unhappiness with what it described as a “late change” proposed by the drug maker. “Agency expressed significant concerns about the changes given the amount of information that was available to influence the decision to alter the statistical analysis plan,” the document says. But there is no indication that the agency put its foot down.

In 2010, when the FDA reviewed the trial as part of its approval process, the agency staff flagged the subject as a cause for caution when interpreting the results. “Moreover, consideration should be given to the late date at which the statistical analysis plan was finalized (essentially after all of the study data had been amassed),” the review said.

At a public meeting, even as she recommended approval of the drug, FDA reviewer Thompson explained her worry to the advisory committee:

“[Y]ou just get a little bit uneasy when things aren’t finalized until later. You sort of, not saying that someone knew something here and changed something, but there is a sense of who knew what and when. And I think really the safest approach in clinical trials is to finalize the statistical analysis plan early, and I think the question is always, well, why don’t they? I mean, you know the design of the trial. You know the endpoints you’re looking at. Why don’t you figure out what you’re going to censor at the start of the trial? Why do you need to wait until all the study data have been amassed?”

“I don’t want to cast aspersions,” she added.

4. The FDA redacted a key document related to its evaluation of Pradaxa in a way that protected the product’s image at the expense of informing the public.

A superficial reading of the clinical trial results might have given the impression that, in certain respects, Pradaxa distinctly and unqualifiedly outperformed the old standard, warfarin. However, when FDA scientists looked beneath the surface, they determined that many patients would have nothing to gain from switching to the new drug. They determined that Pradaxa’s apparent advantage was largely the result of something else going on in the trial: in test subjects taking warfarin, an important variable was controlled unevenly, potentially rendering the warfarin less effective than it could have been and skewing the comparison.

For the public, the agency obscured that point by redacting a key passage in a memo posted on the FDA’s website explaining its decision to approve the drug.

To understand the context, it helps to take a step back.

Clinical trials are supposed to be tightly controlled scientific experiments. But these studies, sponsored by the manufacturers, have evolved into sprawling undertakings with increased potential for quality control to break down.

Over the past two decades, clinical trials with one, two, or three academic centers associated with teaching hospitals have been replaced by multi-center trials in which dozens, scores, or hundreds
of physicians enroll thousands of patients, a handful at a time. The doctors at each of the sites are typically paid for each patient they enroll; the more they enroll, the more money they stand to make. Managing the trials and making sure the doctors are following the trial protocols becomes more difficult when the sites are so scattered. With approximately 18,000 subjects recruited by more than 1,500 health care providers at 951 sites in 44 countries, the Pradaxa trial was a prime example of the trend. More than two-thirds of the patients enrolled in the trial were in foreign countries, including parts of the world where medical standards are lower and quality control may be harder to maintain.\textsuperscript{145}

“I wouldn’t trust, without an audit, any trial that recruits patients from 44 countries,” said former FDA Commissioner David Kessler.\textsuperscript{146}

Patients on warfarin are supposed to have their blood monitored and their dosing managed as needed to keep their blood from becoming, in simple terms, too thin or too thick—in other words, too slow or too quick to clot. One of the goals of the RE-LY trial was to keep the warfarin patients’ blood-clotting time, called INR for International Normalized Ratio, between 2 and 3, meaning that it would take their blood between two and three times normal to clot.\textsuperscript{147} The doctors who enrolled the patients were supposed to watch their INR and adjust their warfarin doses if their scores were too high or too low. In fact, the average amount of time each warfarin patient’s INR rested between 2 and 3, known as Time in Therapeutic Range or TTR, varied dramatically by country. In some countries, clotting times were in the desired range less than half the time. In Taiwan, for example, subjects were in the desired range 44 percent of the time on average. In Sweden, 77 percent.\textsuperscript{148}

During the trial, Boehringer Ingelheim seems to have loosened the standard for measuring clotting levels. On August 7, 2008, Amendment 5 to the trial protocol “removed the failure to measure INR values per protocol as a protocol violation,” according to an FDA document.\textsuperscript{149}

In a sense, the uneven warfarin control may reflect the practical challenges of administering a drug that requires regular blood tests, providing a glimpse of how it performs in the real world.\textsuperscript{150} What is noteworthy is the FDA’s decision to obscure from the public an observation about how the variation in warfarin control affected the results of the clinical trial.

When Thompson, the FDA reviewer, briefed the advisory committee, she said “mortality effects” in the clinical trial were “highly driven” by subjects on warfarin “achieving very low levels or poor levels of INR control.”\textsuperscript{151} She pointed out that it was possible to do a better job of monitoring warfarin in a clinical study, noting that there were “much higher levels of control” in a trial involving a different drug.\textsuperscript{152} Further, she implied that warfarin control in the Pradaxa trial might have been even worse than reported; she noted that some patients in the trial were monitored infrequently, calling into question whether their measurements truly reflected the amount of time their warfarin control was in the desired range.\textsuperscript{153}

In addition, the FDA report Thompson co-authored essentially said that Pradaxa owed its apparent superiority to warfarin in reducing strokes and systemic embolisms to the sites with poorer warfarin control, which made warfarin look worse than it otherwise would have.\textsuperscript{154} Addressing the advisory committee, FDA safety reviewer Nhi Beasley—Thompson’s co-
author—boiled it down to this: “So if you have a patient that is well controlled on warfarin, I would not recommend switching to dabigatran, for the reason of less bleed.”

Ellis Unger, then deputy director of the Office of Drug Evaluation in the FDA’s Office of New Drugs, covered some of the same ground in a memo explaining the agency’s decision to approve Pradaxa. “Despite the apparent overall superiority of dabigatran to warfarin at the 150 mg BID [twice daily] dose in the population as a whole,” he wrote, “the effect was driven entirely by patients in the warfarin group who were not as well controlled with respect to INR.”

“Patients whose INRs were well-controlled with warfarin had the equivalent risk of having a stroke or fatal event as those treated with dabigatran 150 mg. Thus, the superiority is really conditional, and depends on how well warfarin is used,” he wrote.

However, in the version of Unger’s memo the FDA posted on its website, the agency blacked out two sentences following those statements—the part where Unger translated his technical analysis into advice that was blunt, practical, and relatively easy to understand.

The posted version of the memo included a notation indicating that the redaction was intended to protect “trade secrets and commercial or financial information.” (The notation indicated that the FDA was invoking Exemption (b)(4) of the Freedom of Information Act, which would allow the agency to withhold such information.)

When POGO sought the missing text through the Freedom of Information Act, the FDA ceded it: “It is important, therefore, not to provide dabigatran with a superiority claim to warfarin, because it would imply that even those well-treated with warfarin should be switched to dabigatran. Clearly, that is not the case.”

In other words, by misrepresenting the redacted passage as a trade secret or something similarly proprietary, the FDA had tried to avoid public release of an official conclusion that certain patients would not be better off taking the new drug.

POGO found many other suspicious redactions in the publicly released versions of FDA drug review records.

5. After refusing to allow the drug maker to claim Pradaxa was superior to warfarin, the FDA acceded to the company’s wishes and permitted it to make the stronger marketing claim.

When the FDA approved Pradaxa, it refused to give the drug a superiority rating compared with warfarin. It only declared that the new drug was not inferior to the old one. That was enough for Pradaxa to make it to market, but in theory it prevented Boehringer Ingelheim from asserting a potentially valuable marketing claim.

However, at the company’s request, the FDA later changed its mind and agreed to let Boehringer Ingelheim claim that, when it came to reducing strokes, Pradaxa was superior to warfarin. The regulatory agency in May 2012 essentially put aside its own prior concerns about the uneven warfarin control. In a memo, Thompson, one of the same FDA reviewers who originally highlighted the issue, stated that the warfarin control was “reasonable.”
In a parallel to the redaction of Unger’s memo, the FDA also agreed that the manufacturer could delete from the Pradaxa prescribing information sheets—known as the package insert or label—a related paragraph and chart, including this sentence: “The benefits of PRADAXA 150 mg relative to warfarin were most apparent in patients enrolled at centers with INR control below the median.”

The wording—which merely hinted at Unger’s point in comparatively oblique and technical terms—disappeared from the label used to inform doctors about the drug.

Within Boehringer Ingelheim, advance word of the FDA’s decision was greeted with jubilation. In a January 19, 2012, email to colleagues later read aloud in a deposition, Boehringer Ingelheim’s Michelle Kliewer shared the news:

“Great news for Pradaxa. Alison Blaus, FDA, called this morning with a brief outcome of yesterday’s internal FDA meeting regarding our request. … We will receive a letter from FDA to remove Table 6 from the USPI [package insert] and allowing a superiority claim in our U.S. promotional materials. … Alison said there will be no rationale for the change provided in the letter, as they want no discussion with other people/companies.”

6. For years, the FDA allowed Boehringer Ingelheim to make another marketing claim about the drug that the FDA itself eventually concluded was “misleading.”

When Pradaxa debuted on the U.S. market, its manufacturer promoted it with an eye-popping claim: “In a clinical trial, PRADAXA reduced stroke risk 35% more than warfarin.” The statistic “35%”—which appeared in large type—could have given consumers an inflated sense of Pradaxa’s benefits.

In the clinical trial, 3.4 percent of patients taking warfarin had a stroke compared to 2.2 percent of patients taking Pradaxa, the FDA later explained. Boehringer Ingelheim had focused on the fact that 2.2 is about a third less than 3.4, but the absolute difference in stroke rates between patients on the two drugs was only 1.2 percentage points.

After Pradaxa had been on the market for more than two and a half years, the FDA told Boehringer Ingelheim to spell that out. “[W]e are changing our opinion regarding Pradaxa … direct-to-consumer promotional materials which include” the 35 percent claim, the FDA said in a letter to Boehringer Ingelheim. “As presented, the 35 percent relative risk reduction claim is misleading because it does not inform consumers about the absolute magnitude of the benefit of the drug, an important consideration when weighing benefits against risks.”

Without additional context, Boehringer Ingelheim’s statistic “can suggest a magnitude of benefit much greater than demonstrated,” the FDA added.

It is unclear why the FDA ever saw it differently—or why it allowed the 35 percent claim at a time when the manufacturer was barred from claiming Pradaxa was superior to warfarin.
7. The FDA tolerated sloppiness and arguably loose controls in the management of the clinical trial.

Though the very term “clinical trial” may conjure images of pristine science—men and women in white lab coats working with care and precision—POGO found more of a sausage factory.

Initial application rejected

Boehringer Ingelheim submitted its initial application for approval of Pradaxa to the FDA in December 2009, months after its researchers had published the results of the clinical trial in The New England Journal of Medicine. Based on errors the FDA spotted in the application, including numbers it described as “highly implausible,” the agency refused to even consider it.

“The readily identifiable errors in these datasets led to concerns regarding the overall quality of the datasets,” the FDA’s Sharon K. Gershon said in a 2010 memo.

For example, subjects were shown as having received transfusions of 62 units, 82 units, and 92 units of blood in one day, where other documents indicated that they had actually received 2 units each. The numbers were absurd on their face; 92 units of blood would be approximately enough to replace all of the blood in a large horse.

As summarized in the Gershon memo, the drug maker told the FDA that errors “may have resulted from” the use of an optical character resolution system, apparently meaning technology used to scan and input information.

Boehringer Ingelheim agreed to recheck the data, or at least samples of the data. Along the way, it discovered 32 previously undetected heart attacks among trial subjects. It identified 68 additional “major bleeds.” Altogether, it identified previously unnoted adverse events in 108 patients. The quality checks altered thousands of data points—3,743 dose values and 3,856 INR numbers reflecting measurements of clotting levels.

At the end of the process, the FDA reviewers concluded that the data were of “sufficient quality to allow substantive review,” Gershon wrote.

“[T]he conclusions based on revised datasets,” Gershon wrote, “were unchanged from those previously reported with respect to safety and efficacy.”

Even that wasn’t the last word. Four years later, in September 2014, authors of the original Pradaxa study disclosed that an additional review had turned up more adverse events in the clinical trial—strokes and “episodes of major bleeding,” some of them fatal. Some of the cases that came in for fresh scrutiny were identified not by the company that sponsored the trial or the scientists who led it, but rather by lawyers representing plaintiffs in litigation over the drug.

“Taken together, these corrections, and the corrections that were reported previously, do not change the conclusions of the study,” the authors said in a letter to The New England Journal of Medicine.
**Sloppy Science: Inspections document regulatory violations in RE-LY trial**

Clinical trials are generally run by two types of players: The makers of the drugs in question and the companies to which they outsource much of the management, known as Contract Research Organizations (CROs).

For help running the clinical trial of Pradaxa, drug-maker Boehringer Ingelheim enlisted Population Health Research Institute (PHRI), a Canadian organization that specializes in conducting clinical studies. PHRI is affiliated with McMaster University and Hamilton Health Sciences Corp., a hospital group in Ontario.

The way PHRI described the RE-LY trial on its website may be revealing: “The primary objective of this trial is to demonstrate the efficacy and safety of dabigatran etexilate in patients with non-valvular atrial fibrillation for the prevention of stroke and systemic embolism.”

One might hope that the purpose of the study was to *determine* the efficacy and safety of the drug; PHRI’s site said the objective was to “demonstrate” those.

When the FDA inspected Boehringer Ingelheim and PHRI, the agency found that much was amiss.

The FDA and its European counterpart conducted the inspections in August 2010, and the FDA’s Gershon summarized the results in a memo dated October 13, 2010—less than a week before the FDA approved Pradaxa and almost a month after the FDA advisory committee had recommended approval.

According to the memo, an overarching problem was that the legal handoff of responsibilities from the manufacturer to the CRO was not completed in a clear and timely fashion, contributing to a breakdown of accountability. The RE-LY trial ran from approximately November 2005 through March 15, 2009, or April 1, 2009.

The first subject was enrolled on November 30, 2005, or December 20, 2005 (the memo gives conflicting dates). And based on a letter of intent, PHRI was responsible for an array of functions including overall data management, setting up randomization systems, and coding of adverse events. However, the letter of intent did not lead to a signed, legally binding contract between Boehringer Ingelheim and PHRI until July 2007, mid-way through the trial.

The inspection of Boehringer Ingelheim found such “violations” as “failure to ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan,” the FDA memo said. The FDA issued a document called a Form 483 identifying objectionable conditions at Boehringer Ingelheim.

The trial was supposed to follow ethical principles stated in the “Declaration of Helsinki,” which calls for clinical trials to obtain informed consent from participating patients. But the FDA memo said clinical sites involved in the RE-LY trial collected information from and about subjects who had withdrawn consent.

A rulebook for the trial, called the Trial Monitoring Manual, was supposed to be completed and approved before the trial began, but an approved version was not available until March 2007, the
FDA memo says. (The memo doesn’t say who was supposed to approve the manual; it was apparently a different document from the statistical manual discussed earlier in this report.)

An adjudication committee was supposed to judge how adverse events such as major bleeding should be counted, but there was no documentation that a charter was written for the adjudication committee before the first cases were reviewed in December 2006.

The inspection of PHRI found parallel problems, according to the memo. “There were no procedures, plans, or manuals, either written and/or in place prior to performing critical study-related functions, prior to enrollment (December, 2005).” Procedures for reporting significant adverse events were not finalized until October 2006.

As of a final reconciliation in June 2009, there were about 110 significant adverse events in the PHRI database that were not in the Boehringer Ingelheim database. PHRI later told the FDA that those discrepancies “appeared to be resolved,” the memo said.

Though the inspection of PHRI found regulatory violations, no Form 483 was issued to the organization because the contract transferring responsibilities from the manufacturer to the CRO did not become effective until July 2007, the FDA memo said.

PHRI leaders did not respond to questions emailed by POGO in July 2015. Asked in 2014 about the FDA’s examination of its work, Salim Yusuf, PHRI’s executive director, replied: “You really must ask the FDA these questions. We know that the FDA regards the work of the PHRI very highly and has praised us several times.”

8. When doctors helping to oversee the trial were found to have mismanaged their part of it, the FDA’s response appeared toothless.

Under federal law and regulations, investigators in clinical trials are responsible for ensuring that their work is conducted in accordance with the plan or protocol for the trial. Their responsibilities include protecting the rights, safety, and welfare of subjects under their care, and obtaining the informed consent of subjects receiving an experimental drug.

Simply keeping complete and accurate records in clinical trials is so important that even lapses involving certain required paperwork can be grounds for prosecution.

However, when doctors involved in the Pradaxa trial violated standards, the FDA did not restrict their participation in future clinical trials, as far as POGO could determine. At most, it appears, the FDA gave those doctors a warning or reprimand and demanded that they explain how they would avoid repeating their mistakes, based on a review of public records and other documents obtained through the Freedom of Information Act.

Some of those doctors came under FDA scrutiny as a result of audits by Boehringer Ingelheim. The drug maker found that several participating doctors were not in compliance with “Good Clinical Practice” and ended their work in the trial.
The FDA followed up on those audits with inspections of its own. The FDA’s handling of the doctors shows how much the agency is willing to tolerate before disqualifying doctors from participating in clinical trials or, short of that, imposing restrictions on them.

One of the doctors cited in the inspections was a Miami cardiologist named Dov Linzer. His alleged lapses, detailed in an FDA document, included enrolling medically ineligible subjects, not obtaining valid informed consent from patients, not performing or documenting required tests, failing to maintain adequate and accurate case histories, and apparently failing to report adverse events to the RE-LY organizers.

Linzer’s conduct “raises significant concerns with respect to data integrity and how you protected the rights, safety, and welfare of subjects who were enrolled into this study,” the FDA said in a warning letter.

According to the warning letter, the trial protocol specified that subjects with severe renal impairment were to be excluded from the study, but Linzer’s site enrolled such a patient. The protocol specified that patients with liver disease, such as hepatitis, were to be excluded, but without waiting for the results of a patient’s hepatitis test, Linzer’s site had enrolled the patient and had begun treating him or her with the experimental drug. The patient tested positive for Hepatitis C. The protocol specified that patients were supposed to undergo monthly tests of liver function during the first year of treatment, but the FDA said it could not verify that Linzer’s site performed the tests at monthly intervals; one of the patients it listed was missing four months of tests.

The warning letter noted that FDA regulations prohibit using human subjects in clinical trials unless the researcher has obtained the subject’s legally effective informed consent. (The goal of informed consent, a cornerstone of medical ethics, is to make sure human guinea pigs understand what they are getting themselves into, risks and all, before they expose themselves to experimental treatments.) After the informed consent document for the Pradaxa trial was revised to include new information, Linzer’s site failed to “re-consent” 11 subjects in a timely manner using the new disclosure. “The revised informed consent document … provided information that may have affected the subjects’ willingness to stay in the study, because it warned them of additional risks,” the FDA letter said.

According to the warning letter, Linzer failed to promptly inform the drug maker about adverse effects that might have been caused by the experimental drug.

The FDA letter faulted Linzer for delegating his responsibilities to staff members who did not appear qualified, and then failing to supervise them adequately.

The FDA gave Linzer 15 working days to notify the agency “of the actions you have taken or will be taking to prevent similar violations in the future”—even as it criticized corrective steps he had already taken. The letter warned that “failure to adequately and promptly explain the violations … may result in regulatory action without further notice.” An FDA database shows that his inspection results were coded as “OAI”—Official Action Indicated. According to the FDA’s website, the term means: “Objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated.”
More than six years after the inspection, Linzer’s name does not appear in an FDA database of clinical investigators whom the agency has restricted or sought to disqualify from engaging in clinical trials.²¹¹

“I failed many of my responsibilities as the Principal Investigator,” Linzer acknowledged in a 2009 letter to the FDA. “[B]ut presently I am now very informed in the investigational practice and all I want is to be giving [sic] the opportunity to demonstrate my interest in research.”²¹²

Contacted by POGO, Linzer said, “It would be insane for me to talk to you,” before hanging up.²¹³

When the results of the Pradaxa clinical trial were published in *The New England Journal of Medicine* in September 2009, months after the FDA issued the warning letter to Linzer, he was still in the picture. The name “D. Linzer” was listed in an appendix to the *NEJM* article as one of the investigators who recruited at least 12 patients to the RE-LY trial.²¹⁴

The FDA also issued a warning letter to Charles McKay, a doctor in Torrance, California, and former chief of cardiology at Harbor-UCLA Medical Center in Los Angeles.²¹⁵ It said he “failed to have adequate involvement in and oversight of the study to ensure data integrity and to protect the rights, safety, and welfare of subjects enrolled in the study.”²¹⁶

According to McKay’s warning letter, his site was informed that one of his research subjects suffered cardiac arrest, had been hospitalized, and later died. Though McKay’s site knew of the death in September 2007, it was not reported to the trial’s sponsor until November 2008, more than a year later, the FDA found. Another subject was hospitalized several times during the study but the FDA was unable to find documentation that those events were reported to the sponsor. If the FDA’s findings are accurate, the managers of the trial were not given the chance to assess those episodes as they happened, including any implications for the safety of others.

In addition, though subjects were supposed to return to the clinic for follow-up visits at three- and then four-month intervals, four of McKay’s five enrolled subjects were not adequately followed, the FDA said. For two patients, about a year elapsed between visits. Similarly, the FDA said, lab tests were not performed as specified in the protocol. For one patient, the FDA found no evidence that monthly lab tests were performed from October 16, 2007, “to the time the subject terminated from the study on October 24, 2008,” more than a year later.

In an inspection report, FDA investigators summarized what they said McKay told them. “He stated he now knows through the experience of this FDA inspection that there was so much more he needed to know to conduct trials and that he should have hired trained and committed staff from the beginning,” the inspection report says. “He stated he feels very badly and is concerned about this incident of misalignment in his conduct of 20 years of good research.”²¹⁷

Like Linzer, McKay was given 15 working days to explain himself to the FDA, and he was warned that failure to do so could result in regulatory action. McKay’s name does not appear in the agency’s database of disqualified and restricted clinical researchers.

He did not respond to requests for comment for this report.
With respect to both Linzer and McKay, FDA staff determined that their data was so unreliable it should not be used in support of Boehringer Ingelheim’s application for approval of Pradaxa. But, absent further evidence of trouble, the FDA was evidently ready to accept their data in future trials.

POGO asked the FDA to explain what it did when it found deficiencies by investigators in the RE-LY trial. POGO also asked whether any FDA actions against clinical investigators go undisclosed. An agency spokeswoman left that question, along with many others submitted for this report, unanswered.

In addition to inspecting clinical researchers whose sites Boehringer Ingelheim had closed for cause, the FDA inspected several doctors’ sites that the agency independently selected for scrutiny. One of them was Maria Anastasiou-Nana. Anastasiou-Nana ran a site in Athens, Greece, that enrolled 145 subjects in the RE-LY trial. She was also listed as an adjudicator in the trial, indicating that she was responsible for helping to review other researchers’ data and judge how results from other sites should be counted.

Anastasiou-Nana drew the FDA’s attention for several reasons, according to an FDA memo: she ran a foreign site, she enrolled a lot of subjects, she enrolled all of the subjects she screened (implying that, perhaps improbably, all of them met the enrollment criteria), and many of the subjects she enrolled were discontinued. The FDA apparently notified Anastasiou-Nana or Boehringer Ingelheim that it planned to inspect the doctor’s site, sacrificing the element of surprise.

After it learned that the FDA was on its way, Boehringer Ingelheim shared some information that was, according to the Gershon memo, “previously not reported.” The site’s subjects had experienced eight “events” such as stroke or major bleeding.

The FDA inspection of Anastasiou-Nana’s site cited a list of problems including “failure to report all adverse events.”

Gershon’s conclusion: “On assessment of preliminary findings from the inspection, it appears that some or all data may not be reliable from this site. As the field inspector is unavailable to answer questions concerning the pervasiveness of the issues identified during the inspection, final recommendations on data reliability cannot be made at this time. … In the interim, DSI [the FDA’s Division of Scientific Investigations] is unable to confirm validity of the data and recommends that the review division consider excluding the data from this site in their primary evaluation of efficacy and safety.”

Anastasiou-Nana’s name does not appear in the FDA database of clinical researchers who have been restricted or disqualified. An FDA database of inspection results says she was given a code of “VAI,” which stands for “Voluntary Action Indicated.” According to the FDA, VAI means: “Objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntarily.”

Contacted by a journalist in Greece calling on behalf of POGO, Anastasiou-Nana declined to comment.
Anastasiou-Nana’s case also raises questions about the timeliness of the FDA’s inspections. Gershon, who represented the FDA’s Division of Scientific Investigations, relayed the information about Anastasiou-Nana in a memo to FDA reviewers dated October 13, 2010. The Gershon memo suggests that the agency was still trying to sort out this situation almost two months after the FDA staff completed its August 25, 2010, review report on Pradaxa, almost a month after the FDA advisory committee voted unanimously to endorse the drug (September 20, 2010), and mere days before the FDA announced its October 19, 2010, decision approving the drug. The Gershon memo also says that, when the memo was written, the Division of Scientific Investigations had not yet received or reviewed written inspection reports for several of the inspection subjects, including Boehringer Ingelheim and PHRI, the organization that helped manage the clinical trial.

9. Doctors faulted by the FDA in earlier trials participated in the testing of Pradaxa.

The FDA’s handling of offenders in the RE-LY trial was part of a broader pattern. Dozens of researchers the FDA had cited for violating standards in prior clinical trials, including repeat or even three-repeat offenders, were allowed to enroll and monitor patients in the Pradaxa trial, POGO found.

Those findings are based on a review of lists of clinicians who oversaw patients in the RE-LY trial and FDA records, including documents obtained through the Freedom of Information Act.

In 2005, the FDA issued a warning letter to Raymond E. Tidman of Blue Ridge, Georgia, saying in part, “You failed to protect the rights, safety, and welfare of subjects under your care.”

At issue was Tidman’s conduct in a study comparing antibiotics for complicated infections of skin and soft tissue. Among the FDA’s assertions: The trial required that patients be monitored through an array of lab tests, including tests for a protein called CPK. The CPK tests were meant to reveal whether patients were suffering from a breakdown of muscle tissue that could lead to kidney failure. “Despite the importance for subject safety of monitoring CPK levels, and the protocol’s explicit requirements to do so, you did not obtain all required CPK levels or other required laboratory results for any subject you enrolled. ... For some subjects you failed to obtain most of the required CPK levels.”

“Failure to obtain required laboratory results may have exposed your subject ... to an increased and unnecessary risk of serious toxicity,” the FDA said.

In a written response to the FDA dated January 11, 2006, Tidman said subjects were treated at a hospital, and he implied that lapses occurred there. “We have not since relied on non-study hospital staff or other third-parties to carry-out laboratory assessments per physician orders,” he wrote.

“We are able to learn from our mistakes,” he added. “Our response is not to use the third-party hospital as a ‘scape goat.’ On the contrary, we consider it our failure in not recognizing them as unable or unwilling to follow the rigors of clinical care in a research protocol.”

Tidman did not respond to requests for comment for this report.
According to the FDA website, the standard for disqualification from clinical trials is repeated or deliberate failure to comply with applicable requirements. An FDA notice in the Federal Register said that repeated violations can include more than one violation in a single study, and that a deliberate violation can include reckless disregard for the requirements.\(^{243}\) However, POGO found that doctors cited in as many as three past inspections were able to participate in the Pradaxa trial.

Raye L. Bellinger, a California cardiologist, was cited for deficiencies in 1990, 1999, and 2001.\(^{244}\) In each of those inspections, he was faulted for inadequate informed consent. In two of them, he was faulted for failing to follow the investigational plan. And, in two of them, he was faulted for inadequate and inaccurate records. Other deficiencies included failure to report adverse drug reactions. In a 1999 letter, Bellinger “promised correction of the items listed” on an FDA inspection report.\(^{245}\) But similar problems turned up two years later.

Bellinger did not return calls for this report.

Massachusetts cardiologist Terrence Hack, cited by the FDA in 1997 for failing to follow a trial’s protocol and to report adverse drug reactions, was again found to be out of compliance with a trial’s protocol in 1999. Two years after that, another FDA inspection found that he was keeping “inadequate and inaccurate records.”\(^{246}\) Even with three strikes on his record, the cardiologist was permitted to join the RE-LY trial, where he enrolled more than a dozen patients.\(^{247}\)

Hack did not respond to requests for comment.

In some cases, it’s hard to tell how significant the FDA inspection findings were.

Take Jack Hirsh of McMaster University’s Department of Medicine in Ontario, Canada, for instance. He served on the RE-LY data safety monitoring board, a group responsible for making sure that subjects in the RE-LY trial were not being harmed by Pradaxa.\(^{248}\)

In a 1992 FDA inspection, Hirsh was cited for failing to follow a trial’s investigational plan, keeping inadequate and inaccurate records, maintaining inadequate drug accountability, and for a deficiency involving informed consent.\(^{249}\)

Hirsh told POGO that the study in question was completed about nine years before the FDA inspection and was never intended for submission to the FDA. In an email to POGO, Hirsh said he and his colleagues once had but did not keep certain records the FDA was seeking. “Clinical trial methodology is much more sophisticated now and even in the 1990’s than it was in the early 1980’s,” he added.\(^{250}\)

However, in the case of three-time offender Terrence Hack, FDA inspection violations were precursors to other problems and, in hindsight, could have served as red flags.

In a consent order with the Massachusetts Board of Registration in Medicine in September 2006, while the RE-LY trial was under way, Hack admitted to prescribing warfarin to a 74-year-old patient in April 2003 without monitoring her anti-coagulation level. According to the consent order, in May 2003, the patient went to a hospital complaining of blood in her urine, abdominal
pain, dizziness, and vomiting. It turned out that the patient had an elevated INR level and a cerebellar hemorrhage.\textsuperscript{251}

Hack’s consent order says his failure to assess the patient’s anticoagulation level “fell grossly below the standard of care.”\textsuperscript{252} The case showed the potentially grievous consequences for patients when doctors fail to follow proper clinical procedures. The Massachusetts board fined Hack $7,500.\textsuperscript{253} In a follow-up action by the Medical Board of California, Hack agreed to enroll in ethics and education courses.\textsuperscript{254}

In April 2015, Hack was in trouble again—this time, with the Department of Justice. He and his practice, Primary Care Specialists, Inc., agreed to pay $24,000 to resolve allegations that they violated federal law by conducting medically unnecessary nuclear stress tests and billing Medicare for them, according to a press release by the U.S. Attorney’s Office for the District of Massachusetts. The Justice Department said the tests wasted government dollars and needlessly exposed patients to radiation.\textsuperscript{255}

You might think that doctors with checkered inspection records would merit heightened scrutiny from the FDA. However, as far as POGO can tell, less than a week before the agency announced its approval of Pradaxa, an internal FDA summary of clinical investigator inspections the FDA had conducted in connection with the RE-LY trial named only one past offender. (Two names on the list of inspection subjects are redacted, though their site numbers match doctors with no prior inspection violations.)\textsuperscript{256}

Melvin J. Tonkon of Santa Ana, California, was singled out for inspection in the RE-LY trial based on his inspection history, but he died before the examination of his work in RE-LY was completed, according to FDA records. Tonkon had been cited in 1998 for alleged falsification of signatures and failure to report adverse events, according to an FDA document.\textsuperscript{257} (The agency initiated proceedings to disqualify Tonkon from participating in clinical trials in 1998 but ultimately decided not to do so, an FDA database shows.\textsuperscript{258}) After Tonkon died, the FDA carried on with an inspection of work performed in the RE-LY trial under the doctor who took over Tonkon’s research—and it found deficiencies.\textsuperscript{259}

The memo summarizing the FDA’s RE-LY inspections, written by Sharon Gershon of the agency’s Division of Scientific Investigations, shows how few clinical trial sites the FDA inspects. The memo describes FDA inspections of 16 clinical sites\textsuperscript{260}; that’s 16 out of 951 in the RE-LY trial overall,\textsuperscript{261} or 1.7 percent of them. (And Gershon appears to have counted 1 of the 16 twice.\textsuperscript{262})

A POGO analysis found that 32 principal investigators in the RE-LY trial—clinicians who oversaw sites where trial subjects were enrolled—were cited for deficiencies in FDA inspections of earlier trials. That might seem like a small number compared to the total population of 1,023 principal investigators in the RE-LY trial. However, based on POGO’s analysis of an FDA database that goes back to 1977,\textsuperscript{263} only 42 of those 1,023 principal investigators had been inspected by the FDA before the RE-LY trial began.\textsuperscript{264}

In other words, 76 percent of the RE-LY trial principal investigators who had been inspected before that trial were found to have committed errors in earlier trials. If that percentage extended
to the more than 1,500 principal investigators and other clinical investigators in the RE-LY trial, there would have been more than 1,125 past offenders helping to conduct the trial.

(POGO’s analysis focused on the 1,023 “principal investigators” as distinct from the larger set because POGO was only able to obtain detailed identification information for principal investigators.)

Most of the deficiencies noted in RE-LY investigators’ prior FDA inspections were classified as “VAI,” including findings for Terrence Hack. According to the FDA, that means: “Objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntarily.” However, it is often unclear why the FDA classified deficiencies as VAI instead of something more serious.

A broader review of FDA inspection and enforcement records puts the Pradaxa case study in perspective. POGO’s analysis of 10 years of those records shows how rare it is for the FDA to impose sanctions, even when it finds problems of the most serious kinds.

Over a 10-year period—from 2005 through 2014—the FDA conducted 5,115 inspections of 3,120 investigators working on new experimental drugs, according to the agency’s online inspection database.

Of the 3,120 clinical investigators the FDA inspected over that decade, 1,573, or about 50 percent, were cited for deficiencies in their research. Among those, 176 investigators received an inspection code at the most severe end of the scale: “OAI” or “Official Action Indicated.” According to the FDA, OAI means the regulatory violations uncovered were “significant/serious and/or numerous.” Further, it means that human subjects “would be or have been exposed to an unreasonable and significant risk of illness or injury,” that their rights “would be or have been seriously compromised,” or that the “integrity or reliability” of data was compromised.

In the vast majority of cases, however, the FDA took no further publicly disclosed action against the doctors. Over the 10-year period, 95 investigators received warning letters from the FDA office tasked with overseeing clinical drug trials. During that same period, 35 investigators were notified that the agency was initiating proceedings to potentially disqualify them from participation in clinical trials. Of those 35 investigators, 26 were disqualified, 5 had their work restricted, 2 were not disqualified, 1 subsequently had his restrictions removed, and 1 was still awaiting a final determination as of July 2015.

“The standards for disqualification and debarment do little to protect research subjects because investigators and sponsors can engage in a wide range of noncompliance that threatens the rights and welfare of research subjects,” said Elizabeth Woeckner, founder and director of Citizens For Responsible Care and Research, a healthcare watchdog group.

“Why would FDA simply not exclude any investigators who’d had serious problems in a previous trial?” Woeckner asked.
10. The publicly available records of FDA inspection results are less than transparent, shielding clinical trials from public scrutiny and accountability.

The FDA posts warning letters on the Internet. However, in public copies reviewed for this report, the FDA often redacted the name of the clinical trial and the name of the drug being tested. When POGO obtained copies of underlying inspection records through the Freedom of Information Act, the FDA often included similar redactions.

Likewise, the FDA’s online database of clinical investigator inspection results does not identify the clinical trials in which deficiencies were found.275

As a result of the FDA’s disclosure practices, “it is usually very difficult, or even impossible, to determine which published clinical trials are implicated by the FDA’s allegations of research misconduct,” Charles Seife wrote in JAMA Internal Medicine, a publication of the American Medical Association.276

POGO’s research on inspection results often required piecing together information from multiple sources. In some instances, it hit a wall.

When the results of the RE-LY trial were reported in The New England Journal of Medicine, the doctors who enrolled and tracked patients in the study were generally identified by country, last name, and initials—rather than by full name, specific location, and institutional affiliation—which had the practical effect of rendering some of them unidentifiable.277

11. When adverse event reports naming Pradaxa mounted, fueling concern about the blood thinner, the FDA issued statements defending the new drug. But outside experts say the analysis behind those statements was glaringly flawed.

Almost as soon as Pradaxa hit the U.S. market, the FDA began receiving reports of adverse events in patients taking the drug. By October 18, 2011, as the first anniversary of FDA approval approached, the FDA’s “Adverse Event Reporting System” (FAERS) had received more than 10,000 of the reports, covering both death and non-death cases, according to data from adverseevents.com.278 Patients were showing up in emergency rooms with serious hemorrhages, and doctors were at a loss.279 In time, a pile of lawsuits was filed against the drug’s manufacturer, and personal injury lawyers began searching for victims by airing television ads.280

In a letter to the editor published in The New England Journal of Medicine in November 2011, three Houston doctors added their voices to the alarm. They said that “life-threatening bleeding complications can occur” when patients on the drug are injured.281

“Recently, we have cared for several injured patients receiving dabigatran, all of whom had poor outcomes,” doctors Bryan A. Cotton, James J. McCarthy, and John B. Holcomb wrote. “Currently, the only reversal option for dabigatran is emergency dialysis (as suggested in a single line in the package insert). The ability to perform rapid dialysis in patients with bleeding whose condition is unstable or in those with large intracranial hemorrhages will present an incredible challenge, even at level 1 trauma centers,” they wrote.282
Though the Houston doctors were focused on hemorrhages triggered by traumatic injury, many of the adverse events involved seemingly spontaneous bleeding from the gastrointestinal tract.

The Pradaxa situation illustrated the difficulty the FDA has had determining whether drugs are causing unforeseen problems once they are approved for use in the population at large. For signs of trouble, the FDA historically depended mainly on reports submitted from the field by the public, the medical establishment, and the manufacturers. Though manufacturers are required to pass such information to the FDA, adverse event submissions by others are voluntary. Only a small but unknown fraction of adverse events may ever get reported, experts say. What’s more, the adverse event reporting system is unable to put the number of reports in perspective because it has no way of tracking how many people are taking the drugs in question. And the reports may leave out important details.

The reports do not prove that a particular drug caused an adverse event. But FDA officials say that drawing such a connection is less of a leap in the case of anticoagulants and serious bleeding.

“Hemorrhaging is not a particularly common spontaneous event,” Dr. Gerald Dal Pan, director of the FDA’s Office of Surveillance and Epidemiology, told POGO. “The bleeding is attributable to the drug. There’s no doubt about that,” said Robert Temple, deputy director for clinical science at the FDA.

Key questions facing the FDA were whether adverse events were occurring at a higher rate than the clinical trial predicted and whether the new drug was proving to be more dangerous than the old one, warfarin. For those answers, the FDA turned to one if its most important new technologies, a data-mining tool known as Mini-Sentinel.

In 2007, after the painkiller Vioxx was associated with heightened risk of heart attack and stroke, Congress ordered the FDA to build a better system for monitoring the safety of products the FDA has approved. The so-called Sentinel post-market surveillance system remains a work in progress, and Mini-Sentinel was an early “pilot” piece of it. Unlike the adverse event reporting system, which depends on information that comes in over the transom, Mini-Sentinel could access health insurance claims data and other medical information, such as diagnosis codes, on millions of patients—178 million as of December 2014. When adverse event reports raised suspicions about products, Mini-Sentinel was supposed to help the FDA resolve them. Pradaxa became an important early test of the FDA’s evolving drug-monitoring capabilities.

On November 2, 2012, the FDA issued a “Drug Safety Communication” reporting its conclusions—and essentially dismissing the alarm about Pradaxa. “The results of this Mini-Sentinel assessment indicate that bleeding rates associated with new use of Pradaxa do not appear to be higher than bleeding rates associated with new use of warfarin, which is consistent with observations from the large clinical trial used to approve Pradaxa (the RE-LY trial).”

The FDA said that, in its assessment, the incidence of gastrointestinal hemorrhages was higher for new users of warfarin than for new users of Pradaxa—1.6 to 2.2 times higher.

“FDA has not changed its recommendations regarding Pradaxa,” the FDA said. “Pradaxa provides an important health benefit when used as directed.”
(The “Drug Safety Communication” included a section of background information on Pradaxa for patients. It did not mention the lack of an agent to reverse the drug’s anticoagulant effect. Instead, in apparent understatement, it said: “Be aware that while taking Pradaxa you may bruise more easily, and it may take longer for any bleeding to stop.”

Five months later, the FDA repeated and elaborated on its conclusions in The New England Journal of Medicine. The FDA argued that the wave of adverse event reports reflected a phenomenon called the Weber Effect: Precisely because they are novel and medical professionals may not know what to expect from them, the theory goes, newly introduced drugs are likely to generate more reports than ones that have been on the market for a long time. The FDA added that “legal activity” and “published case reports” can increase reporting rates.

“We believe that the large number of reported cases of bleeding associated with dabigatran provides a salient example of stimulated reporting,” the FDA said. “In this case, such reporting provided a distorted estimate of the comparative bleeding rates associated with dabigatran and warfarin in clinical practice.”

The journal article and the Drug Safety Communication each included a caveat. The article said there were “limitations” to the FDA’s analysis, “including lack of adjustment for confounding variables.” The safety communication put it more simply: “The estimates do not account for possible differences in the patient populations for the two drugs that may relate to bleeding outcomes, such as age and the presence of other medical conditions.”

Critics said that caveat made the FDA’s analysis worthless. The “confounding variables,” they said, could have turned the conclusion upside down.

Jerry Avorn, a professor at Harvard Medical School and chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women’s Hospital, leveled that assessment in Circulation, the journal of the American Heart Association. If the patients in the FDA study who were prescribed dabigatran were disproportionately young and male compared with those taking warfarin, “an analysis unadjusted for age or gender could make dabigatran appear to be safer than it is, a finding that would be useless or misleading,” Avorn wrote. The absence of any adjustment for such characteristics “made the analysis unsuitable for informing the care of patients,” he wrote.

(Avorn brought a special perspective to the subject. According to Circulation, in 2012, he served on the Sentinel Safety Science Committee advising on the use of data.)

David Madigan, professor of statistics and dean of the Faculty of Arts and Sciences at Columbia University, called the FDA’s Pradaxa study “junk.” He said that, for various reasons, doctors might prescribe Pradaxa for patients who are at a lower risk of bleeding, thereby making Pradaxa look better than warfarin with regard to bleeding. Analyses such as the FDA’s “make little or no evidentiary contribution,” Madigan, who consulted for plaintiffs’ counsel in litigation over Pradaxa, told POGO in a May 2013 email. “I find it disturbing that these analysis [sic] are presented as evidence of safety. In fact what we really have is an absence of evidence.”

In May 2014, a year and a half after the FDA released its Mini-Sentinel study, the agency issued another study of Pradaxa that painted a different picture. The newer study, which was based on a
larger and older patient population, found “an increased risk of major gastrointestinal bleeding with use of Pradaxa as compared to warfarin.” That finding seemed to underscore the trouble with the FDA’s earlier assessment.\(^\text{302}\)

However, the FDA said that, in the newer study, Pradaxa showed advantages on other measures: lower risk of clot-related strokes, bleeding in the brain, and death. It said that gastrointestinal hemorrhage finding was consistent with the clinical trial results that provided the basis for Pradaxa’s approval. “As a result of our latest findings, we still consider Pradaxa to have a favorable benefit to risk profile and have made no changes to the current label or recommendations for use,” the FDA stated.\(^\text{303}\)

The FDA’s market surveillance capabilities have been advancing; the agency has been transitioning from the pilot Mini-Sentinel system to the more mature Sentinel system.\(^\text{304}\) As a reflection on the FDA’s posture as a protector of vulnerable patients, the issue is less the limitations of the agency’s evolving technology than it is the judgment the FDA showed in applying that technology and interpreting the 2012 results for the public.

12. Though Pradaxa can cause fatal bleeding, and though there is no antidote, the FDA has not required the drug to carry a conspicuous “black box” warning about those hazards like the warning applied to warfarin.

One of the strongest steps the FDA can take to alert doctors and patients about a drug’s hazards is to require a “black box warning.” The warning appears not on the actual bottle or package, but at the top of the folded sheet of paper known as the product label or package insert, which may be familiar to prescription users for its technical terminology and fine print.

Many patients no doubt toss the label in the trash. Even harried physicians may not take time to digest all the complicated information it contains. “I’ve not yet met a clinician who’s read a product label,” Darren McGuire, a Texas cardiologist who sat on the FDA advisory committee that recommended approving Pradaxa, told fellow committee members.\(^\text{305}\)

Still, warnings that are in bold capital letters surrounded by a black border are harder to miss.

Black boxes are not common, but neither are they rare. Birth control pills carry boxed warnings that they can cause fatal blood clots. Well-known drugs whose labels carry boxed warnings about risks they pose include Advair Diskus, Seroquel, Effexor XR, OxyContin, Lexapro, Celebrex, Levaquin, and Adderall XR.\(^\text{306}\)

Warfarin, also known by the brand name Coumadin, acquired a black box in 2006. “WARNING: BLEEDING RISK,” the message proclaims. “Warfarin sodium can cause major or fatal bleeding.”\(^\text{307}\)

When Pradaxa was approved in October 2010, it would have made sense to immediately place a similar black box warning on the Pradaxa label—if not a more extensive one. Like warfarin, Pradaxa posed a bleeding risk. Unlike warfarin, Pradaxa lacked a reversing agent. But Pradaxa’s maker, Boehringer Ingelheim, did not voluntarily include such a warning, and the FDA did not invoke its authority to require one.\(^\text{308}\)
The danger was acknowledged, though not in the most logical or conspicuous ways. In a section on warnings and precautions, the label said: “Risk of bleeding: PRADAXA can cause serious and, sometimes, fatal bleeding.” That much was sensible. But, oddly, the lack of an antidote was not mentioned under the heading “WARNINGS AND PRECAUTIONS.” It was noted deeper in the fine print, on the fourth page, under the heading, “OVERDOSAGE”—as if it were of no relevance to patients taking the prescribed dose.

“There is no antidote to dabigatran etexilate or dabigatan,” Section 10 of the label said.

Not until January 2012, more than a year after Pradaxa was approved for the U.S. market, did such a warning appear in the “WARNINGS AND PRECAUTIONS” section, and even then it was relegated to page four of the label instead of being featured on the first page in a summary that highlighted selected warnings and precautions. “A specific reversal agent for dabigatran is not available,” the addition to the “WARNINGS AND PRECAUTIONS” section said.

Asked why there was no black box warning on the original Pradaxa label, Robert Temple, deputy director for Clinical Science at the FDA’s Center for Drug Evaluation and Research, told POGO, “Well, because everybody knows anticoagulants make you bleed.”

He added: “And I think everybody knows that dabi doesn’t have a reversal agent.”

Maybe not everybody.

Mary Denham, whose elderly father Sidney Denham bled to death at a Savannah hospital in 2011, said her family did not know there was no antidote. “We didn’t know that … if he got into trouble with a bleed there wouldn’t be anything to counter it, like Coumadin. … It was kind of portrayed like it’s a win-win,” she said. She expressed incredulity that the drug had been allowed on the market under that circumstance. “How do you let a medication be out there where there’s not something that you can counter it if something bad happens?” she asked. “Nobody else should have to see their father die like that.”

In addition to approving the Pradaxa label, which includes a lot of technical information for doctors, the FDA approved a document called the “Medication Guide,” which is written in plainer language and is geared specifically toward patients. “Read this Medication Guide before you start taking PRADAXA and each time you get a refill,” the January 2015 version says, adding, “This Medication Guide summarizes the most important information about PRADAXA.”

“Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding,” it says, listing symptoms such as “bleeding that is severe or you cannot control.”

The Medication Guide does not mention that your doctor has no antidote.

Neither did another document written for patients—an informed consent form meant to ensure that subjects in the RE-LY clinical trial of Pradaxa were aware of the risks when they enrolled in the study and essentially agreed to become human guinea pigs. (The principle of obtaining informed consent from research subjects is so important that the form must be signed by the patient. The copy Boehringer Ingelheim gave POGO from the RE-LY trial—a 10-page document
marked “Consent Version #7” and dated “14-Feb-2008”—also includes space for the signature of an impartial witness.\(^{318}\)

In contrast, a document titled “Clinical Trial Protocol,” which explained the study and its requirements to participating doctors, said: “There is no specific antidote to counteract the antithrombotic activity of dabigatran etexilate.”\(^{319}\)

Following Pradaxa’s approval, the text of the drug’s FDA-approved label was changed from time to time. Doctors and patients were advised, for example, to open only one bottle of Pradaxa at a time,\(^{320}\) that the drug could cause welts,\(^{321}\) and that administering Vitamin K, commonly used to reverse warfarin’s effects, would not reverse Pradaxa’s effects.\(^{322}\)

It wasn’t until April 2013, after two and a half years on the market and appearances in thousands of adverse event reports, that Pradaxa finally got a black box warning.\(^{323}\) But, unlike the warfarin box, the Pradaxa warning said nothing about the risk of “major or fatal bleeding” or the lack of a reversing antidote.\(^{324}\) As noted by the Institute for Safe Medication Practices, the only warning this black box contained was about the risk of stopping Pradaxa.\(^{325}\)

“Discontinuing PRADAXA places patients at an increased risk of thrombotic events,” the black box said, referring to the formation of blood clots and the strokes that can result. “If anticoagulation with PRADAXA must be discontinued for a reason other than pathological bleeding, consider coverage with another anticoagulant.”\(^{326}\)

In April 2014, Pradaxa’s black box warning was expanded incrementally to include the risk of hematomas in patients who receive spinal punctures or injections such as epidural anesthesia.\(^{327}\)

13. Members of the FDA advisory committee that unanimously endorsed Pradaxa had extensive ties to the pharmaceutical industry. Two went on to receive substantial compensation from the maker of Pradaxa.

In September 2010, Texas cardiologist Darren McGuire joined other members of a standing FDA advisory committee in voting for approval of Boehringer Ingelheim’s drug.\(^{328}\)

Three years later, a financial disclosure McGuire completed for a medical journal said he received “personal fees from Boehringer Ingelheim.”\(^{329}\)

Those weren’t all. The disclosure said he had also received compensation from drug-makers Janssen, Sanofi Aventis, Genentech, Merck Sharp and Dohme, Daiichi Sankyo, Lilly, Novo Nordisk, F. Hoffmann La Roche, GlaxoSmithKline, Takeda, and Bristol-Myers Squibb, plus several firms that assist drug companies with clinical trials.\(^{330}\) Another online disclosure listed financial relationships with additional pharmaceutical companies, including Pfizer, AstraZeneca, Regeneron, Orexigen, and Roche.\(^{331}\)

When the FDA is deciding whether to approve a drug, it frequently turns to outside advisors for guidance. The advisory committee reviews are a significant step in the process. The committees hear presentations from the FDA staff and the maker of the experimental drug, ask questions,
and debate issues. The FDA generally follows their recommendations. But members of those committees are often steeped in the work of the pharmaceutical industry.

That experience could make them more sophisticated advisors. It could also make them identify to a greater degree with the industry they are helping the government oversee. It reflects the fact that drug companies have cultivated relationships with doctors and that many doctors participate in clinical research; it also means that to some extent their bread is buttered by industry in the form of consulting fees, speaking fees, grants, other compensation, and funding for the institutions where they work.

The advisory committee that reviewed Pradaxa, the Cardiovascular and Renal Drugs Advisory Committee, weighed pros and cons and discussed a variety of concerns. In the end, the committee overcame its concerns and voted nine-to-zero to endorse the drug.

Two of the committee’s members had consulted for Boehringer Ingelheim before the panel met to consider Pradaxa, according to disclosures in journal articles; they stayed out of the review.

The committee member who was perhaps most outspokenly skeptical or critical of the RE-LY trial during the advisory committee meeting, Steven Nissen, has taken an unusual posture toward consulting fees and the like: He has reported serving as an unpaid consultant to several drug companies, including Boehringer Ingelheim, and his bio on the website of the Cleveland Clinic says he directed a company “to donate all compensation to not-for-profit causes or to the Cleveland Clinic to support research and education.”

By email, Nissen told POGO that he accepts reimbursement from industry for his direct out-of-pocket expenses but no honoraria, speaking fees, or other personal income. According to a federal database, in 2013, he received a total of $1,114.34 from Boehringer Ingelheim in categories labeled food and beverage and travel and lodging.

“I don’t accept income from pharma because I don’t want to be influenced by personal gain,” he said.

He has chaired several clinical trials for drug companies such as Eli Lilly, Amgen, and Pfizer, and he discloses that he has received grants from them.

Another member of the advisory committee that reviewed Pradaxa, Sanjay Kaul, received payments from Boehringer Ingelheim in 2013 totaling more than $21,000, according to the relatively new federal database called “Open Payments.” The payments fell in categories for food and beverage, travel and lodging, and, primarily, consulting, according to the database.

In 2014, the database says, Kaul’s payments from Boehringer Ingelheim Pharma and Boehringer Ingelheim International totaled almost $75,000.

Kaul, a medical professor at UCLA and cardiologist at Cedars-Sinai Medical Center in Los Angeles, did not answer recent questions about his financial ties.
As for McGuire, a biography of him online says he “is actively involved in the leadership of numerous international clinical outcomes trials.” Like Kaul, he apparently went from advising the FDA on the Boehringer Ingelheim blood thinner to advising Boehringer Ingelheim.

A financial disclosure accompanying a journal article he co-authored in December 2010, three months after the Pradaxa review, did not list any compensation from Boehringer Ingelheim. That seems to have come later. For example, it showed up in disclosure forms McGuire completed in 2013 for the International Committee of Medical Journal Editors. Those do not say how much money he received, and they include only this explanation of what his Boehringer Ingelheim fees involved: “Advisory board; clinical trial executive committee.”

However, some information about money he received from drug companies can be found in the Open Payments database. More can be found in an online database maintained by the University of Texas Southwestern Medical Center, where McGuire is listed as holding three positions: professor of internal medicine, director of the Cardiology Clinical Trials unit, and director of the Parkland Hospital and Health System Outpatient Cardiology clinics. The Texas database, which excludes income from sources such as UT Southwestern itself, is meant to identify potential conflicts of interest. Over a recent three-year period covered by the online database, McGuire’s compensation from Boehringer Ingelheim—reported in dollar ranges and in categories labeled “Consulting, Advisory or Speaking” and “Reimbursements”—totaled between $75,000 and $134,994.

At both the upper and lower end of that range, his compensation from Boehringer Ingelheim exceeded the corresponding totals for each of the other 29 listed sources (mainly drug companies). While he received compensation from many drug companies, Boehringer Ingelheim stood out as a leading source of income.

Over the same period, McGuire’s compensation from all the listed sources totaled between $325,000 and $952,904, according to the database. (The UT Southwestern database categorized each of McGuire’s 2014 financial relationships as posing “No Conflict,” though in the past some were listed as “Under Management Plan.”)

Since 2013, McGuire has served as “Study Co-Chair” of the “CARMELINA international randomized trial,” according to a curriculum vitae for McGuire last updated in January 2014. According to a federal website, the CARMELINA trial is studying a diabetes drug and is sponsored by Boehringer Ingelheim. Beyond any financial benefits, leadership roles in such studies can confer professional prestige.

McGuire’s UT Southwestern bio says that, though he is no longer a member of the FDA’s Cardiovascular and Renal Drugs Advisory Committee, he serves as an “ad hoc consultant” for the committee.

The Project On Government Oversight requested an interview with McGuire and sent him a list of questions. Among other things, we wanted to learn more about his relationship with Boehringer Ingelheim and to hear his views as to what the public should think about such relationships.

McGuire responded with a brief email. “Thanks for the invitation,” he said, “but I will pass on comment.”
14. Former FDA advisory committee members helped Boehringer Ingelheim prepare for its appearance before the FDA’s Cardiovascular and Renal Drugs Advisory Committee, further blurring lines between the regulatory system and the interests it regulates.

In the run-up to the advisory committee meeting that helped determine Pradaxa’s fate and boost Boehringer Ingelheim’s fortunes, Boehringer Ingelheim insiders held a practice session in which outside experts played the role of advisory committee members. A transcript of the rehearsal, labeled “Mock Q&A Session,” was filed in court during the litigation.353

Leading the session was Peter Kowey, a doctor and professor of medicine in Pennsylvania who had spent years on FDA advisory committees, including the Cardiovascular and Renal Drugs Advisory Committee.354

Kicking off the Boehringer Ingelheim Mock Q&A, Kowey made it clear that he was trying to make the session realistic. “[F]or the next hour, hour and a half or so, we’re going to take questions from the committee,” he said, according to the transcript. “[W]e’re going to stay in role,” he added.355

Another panelist at the Boehringer Ingelheim practice session was Craig M. Pratt, a Houston cardiologist who formerly chaired the FDA’s Cardiovascular and Renal Drugs Advisory Committee.

The transcript of the Pradaxa rehearsal shows Pratt quizzing members of the Boehringer Ingelheim team and coaching them on their presentation for the FDA advisory committee. According to the transcript, at one point in the back-and-forth, he advises that Boehringer Ingelheim not spend too much time dwelling on the fact that, in the clinical trial, Pradaxa was compared to warfarin on an unblinded or “open label” basis: “I think you don’t need to spend a lot more time apologizing or explaining why you did an open label trial. I think all the energy is spent saying, this is the data we have; we’re proud of it and this is why we think it didn’t lead to ascertainment bias.”356

FDA Advisory Committee hearings are high stakes affairs, and experts who have advised the FDA have also made it their business to advise drug companies on the FDA approval process.

A news release issued in 2000 summarized Pratt’s background and showed what at least one medical company thought he brought to its table.

“Dr. Pratt is widely recognized for his knowledge of FDA regulatory procedures, particularly in the area of cardiovascular disease,” a company called Vasogen said when it announced that he was joining its Scientific Advisory Board. “Dr. Pratt’s extensive expertise in regulatory affairs and the design, management and interpretation of clinical trials in cardiovascular disease will be a major asset to Vasogen,”’ Dr. Eldon Smith, a Vasogen executive, said in the news release.357

Similarly, a news release issued in 2008 showed what a medical company thought Kowey had to offer—and how extensively Kowey’s multi-faceted career was intertwined with industry.

“He spent nine years as a member of the Cardiorenal Drug Advisory Committee, four years on the Cardiovascular Devices Committee of the U.S. Food and Drug Administration, and … serves
as an ad-hoc consultant to 94 organizations, including many of the largest pharmaceutical companies in the world, such as Pfizer, Merck, GlaxoSmithKline, Amgen, Eli Lilly and Company, and Bristol-Myers Squibb,” a company called NewCardio Inc. said in the 2008 news release announcing his appointment to its advisory board. “His experience with clinical studies and his relationship with more than 60 leading pharmaceutical companies will be of particular interest to NewCardio as the Company continues the commercialization of its lead product,” NewCardio said.358

Kowey is chief of the cardiovascular diseases division at Main Line Health, a Pennsylvania hospital and outpatient care system.359

Kowey told POGO that rehearsal sessions like Boehringer Ingelheim’s have become routine for companies facing FDA advisory committee meetings, and one way companies prepare is “they get people who have been on advisory committees.”360 He said he served on advisory committees in the 1980s and 1990s and in more recent times has been participating in about five or six rehearsal sessions annually. He said that, since his service on advisory committees ended, he has also represented companies before actual advisory committees.

“I don’t say anything that I don’t ardently believe,” he said, adding that he has strived to advance good therapies for patients.361

Craig Pratt holds multiple positions, including professor of medicine at Weill Cornell Medical College, medical director of the Cardiac Care Unit and EKG lab at Houston Methodist Hospital, and director of research in the Houston Methodist DeBakey Heart & Vascular Center, according to a bio on the Houston Methodist website.

“He is a consultant to the Center for Drug Evaluation and Research for the Food and Drug Administration (FDA),” the Houston Methodist bio says.362

In an interview, Pratt said he was probably asked to participate in Boehringer Ingelheim’s Mock Q&A because of his FDA experience. He said he was paid to participate and took a day off of his normal job to do so. He said he brought to the task special knowledge “about the most straightforward and honest way to present your data,” adding, “We try to get them to tell their story faithfully and honestly.”363

In 2012, Pratt co-authored an article in the Houston Methodist DeBakey Cardiovascular Journal comparing Pradaxa, warfarin, and other new anticoagulants.364 The article did not disclose Pratt’s paid participation in the Boehringer Ingelheim rehearsal. To the contrary, it carried this note:

“Conflict of Interest Disclosure: The authors have completed and submitted the Methodist DeBakey Cardiovascular Journal Conflict of Interest Statement and none were reported.”365

In a system where doctors have ties to both the regulatory agency and the regulated industry, Pratt’s disclosure sheds light on attitudes about what does or does not constitute a conflict of interest.

Asked about the fact that the article does not disclose his role in the Mock Q&A, Pratt said: “I don’t think they were close together, and I have no problem with the fact that I didn’t report it.”366
FDA advisory committee members typically serve as “Special Government Employees,” a status that enables them to serve both government and industry at the same time. The FDA screens them for conflicts of interest before each committee meeting, but the screening process and the financial disclosures they make to the FDA are shrouded. The influential role committee members play at the FDA makes them targets of keen interest for pharmaceutical companies and candidates for a revolving door.

For example, a firm called 3D Communications promotes its “FDA Advisory Committee preparation services,” which include “Profiling FDA Advisory Committee members” and “scripting the ADCOM [Advisory Committee] presentation,” according to the firm’s website.

In 2013, 3D Communications announced that it had formed a Cardiovascular Advisory Board “to further support 3D’s work in preparing clients for FDA regulatory submissions and advisory committee meetings.” The board was made up of “current and former FDA Advisory Committee members,” among others, 3D said.

According to 3D’s news release, the board included Kowey and two members of the FDA advisory committee that reviewed Pradaxa—Sanjay Kaul and Darren McGuire.

McGuire, the firm said, had recently finished his term on the FDA’s Cardiovascular and Renal Drugs Advisory Committee. Kaul had recently finished his term on that committee “and is a frequent temporary voting member of the Endocrine and Metabolic Drugs Advisory Committee,” 3D said.

(In fact, Kaul showed up as a temporary member of the Cardiovascular and Renal Drugs Advisory Committee as recently as October 30, 2014, when the committee met to review another new anticoagulant.)

The 3D news release identified a fourth member of 3D’s cardiovascular panel as William Hiatt of the University of Colorado Denver School of Medicine, “a current member of the FDA’s Endocrinologic and Metabolic Advisory Committee” and “the past Chair of FDA’s Cardiovascular and Renal Drug Advisory Committee.”

Contacted by POGO, Hiatt said he “never really agreed” to serve on the 3D board and was upset to be named in the news release. He said that, after the release was issued, he had himself removed from the board without having done any work for it. He said he wanted to avoid something that he felt “crossed the line a little bit.”

Hiatt, who is still on an FDA advisory committee, added in a later interview that he would turn down opportunities like the 3D panel even after ending his service at the FDA. “It’s an easy ‘No’ because it’s a direct conflict,” Hiatt said. “My moral compass sort of guides me against it.”

Hiatt’s approach to potential conflicts of interest and his thinking about them nonetheless underscore how hard it has become to separate the regulatory establishment from the interests it regulates.

“Ideally, if you had people serving on these [FDA] committees who had absolutely no relationship with industry at all, then you might be a little more removed” from “biases” that
“creep in at all kind of levels,” he said. “If you have zero conflicts, then I think you bring a certain naivete to the process, and that concerns me as well,” he added.376

Hiatt said he does not accept personal compensation from pharmaceutical companies, but he explained that a research institute that he heads receives millions of dollars of funding from drug makers.377

Though Hiatt said he would have been uncomfortable helping drug companies prepare for FDA advisory committee meetings as a member of the 3D panel, he said he advises companies on their dealings with the FDA and represents them at public and non-public FDA meetings as part of the work his institute performs under its contracts with drug companies.378

“I’ve gone on many occasions to the FDA on behalf of an industry sponsor to talk about trial design,” Hiatt said. “Many of us also will prepare presentations for FDA advisory committee meetings and represent the industry sponsor at the advisory committee on a study we were involved” with, he said.379

Among the topics on which Hiatt said he advises companies: “how to have conversations with the FDA.”380

15. The FDA approved Pradaxa without a system to test patients’ blood and tailor dosing.

In a television ad for Pradaxa, these words fill the screen: “Unlike warfarin NO regular blood tests.”381

The absence of such testing was a key selling point for Pradaxa when the manufacturer made its pitch to the FDA and when the company advertised the drug to consumers.

But the absence of such testing was potentially a disadvantage as well as an advantage: It left doctors and patients without a system for checking or calibrating the drug’s effect. And disclosures since the drug was approved suggest that some form of testing might have value for some Pradaxa patients. Those disclosures make the FDA’s handling of Pradaxa appear even more questionable. They also underscore the importance of tough regulators, healthy skepticism, and thorough probing when the FDA reviews a manufacturers’ claims.

By way of context, when Boehringer Ingelheim briefed the FDA advisory committee on Pradaxa in September 2010, one of the company’s speakers, a co-chair of the RE-LY study, drew a contrast between the new drug and warfarin, saying warfarin “requires frequent monitoring and is difficult to maintain in the therapeutic range.”382 Explaining why the world could use a new alternative to warfarin, another leader of the RE-LY clinical trial cited warfarin’s “relatively narrow therapeutic range” and the associated “need for lifelong monitoring … and frequent dose adjustments.”383

During the advisory committee meeting, Tom Simon, the patient advocate on the committee, asked the company, “And then lastly, you mentioned the difficulty in monitoring warfarin. How do you monitor your drug?”384
Boehringer Ingelheim’s Paul Reilly replied: “Obviously RE-LY was run without monitoring dabigatran. It was a fixed dose and no attempt was made to control the dosing using anti-coagulation testing.” Reilly went on to mention tests that could be used, but he added that at least some of them are “not that widely available.”

Contacted for this report, Simon said: “The one concern I had—and I voted for it [approval of Pradaxa]—was that I didn’t understand how anybody could take a drug that thins the blood and not check it.”

“I was convinced enough that … the drug was safe, but I did put in that caveat, that there’s no monitoring at all,” Simon added. “I was just a little leery.”

At the committee meeting, Texas cardiologist Darren McGuire zeroed in on the lack of monitoring, and he suggested that another trial be done to evaluate titrated doses. He said such research might point to “a whole spectrum of therapeutic options, like Coumadin, where we can personalize the anticoagulant strategy to optimize risk and benefit.”

But neither the advisory committee nor the FDA sought to delay approval of Pradaxa pending further study. If the lack of monitoring caused the advisory committee any concern, it managed to get over it. And the FDA compounded any associated risk by approving what was essentially a one-size-fits-all dose. Though the manufacturer had sought approval of two twice-daily Pradaxa dosages—150 mg and 110 mg—the FDA approved only the 150 mg version and an exception of 75 mg for patients with renal dysfunction.

Subsequently, the litigation against Boehringer Ingelheim brought additional information to light.

Citing internal company emails, a federal judge wrote that a “high-level scientist” for Boehringer Ingelheim had concluded “that both safety and efficacy of dabigatran are related to plasma concentrations and … that there is a therapeutic range for Pradaxa.” The judge described an effort within the company to keep that conclusion from being published. In addition, he excoriated the company for failing to preserve the files of the scientist, Thorsten Lehr, at a time when the company had a legal obligation to prevent the destruction of potential evidence.

“The emails … may lead a reasonable person to infer a motive for the defendant to abstain from placing a litigation hold on his materials,” Judge David R. Herndon wrote in December 2013.

A draft of a paper on which Lehr is listed as a co-author, which was unsealed by the court, says that “adjusting the dose … to attain an optimal plasma concentration range may further improve the benefit-risk ratio.” It adds that “[m]onitoring of plasma concentrations or antithrombotic [anticlotting] activity … would be required to identify” patients whose extremely high or low plasma concentrations put them at higher risk of major bleeding or stroke.

The information about a therapeutic range for Pradaxa surfaced in December 2013 as the judge fined Boehringer Ingelheim $931,500 for failing to preserve or turn over in a timely fashion internal records sought by plaintiffs in the product liability litigation—records that could serve as evidence in the case. The judge found that Boehringer Ingelheim had engaged in “a clear pattern of numerous and substantial violations,” and he wrote that he was “frustrated beyond comprehension” with the company’s “astounding” conduct.
“The Court is continuously being called upon to address issues relating to untimely, lost, accidentally destroyed, missing, and/or ‘just recently discovered’ evidence,” the judge wrote. The destroyed evidence, the judge wrote, included records kept by Lehr, who “played a vital role in researching Pradaxa.” In a 2012 email, another Boehringer Ingelheim employee described Lehr as “our company expert for dabigatran.”

The judge’s order served as reminder that the FDA might hope for the best of intentions on the part of drug makers, but it should not count on them.

The judge noted that, according to the steering committee of plaintiffs’ lawyers, Boehringer Ingelheim never identified Lehr in answers to its interrogatories, and Lehr was not on a list the company provided of records custodians with relevant knowledge. The plaintiffs learned of his relevance in September 2013 when his name came up in a deposition of another Boehringer Ingelheim employee, the judge wrote. The company later explained that Lehr had not been identified as a custodian when he left the company in 2012 and therefore his records were not placed on litigation hold, the judge wrote. All that remained were his emails, the company told the court.

A group of company emails from 2011 and 2012—after Pradaxa had been approved—reflected an internal debate over whether a scientific paper being drafted by Lehr should include his conclusions about Pradaxa’s therapeutic range, the judge wrote. An email from another company employee “seems to require a revised version of the exposure paper without inclusion of the therapeutic range levels suggested by Prof. Lehr,” the judge wrote. An email from a third company insider “confirms that,” the judge added.

The judge quoted from an email by yet another company insider, Paul Reilly—one of the same people who briefed the FDA advisory committee in 2010: “I have been facing heavy resistance internally on this paper about the concept of a therapeutic range, at least stating it outright.” In an email from June 2012, Reilly wrote that the manuscript “has been ‘on hold’ for almost 6 months.”

Resistance was on display in a February 2013 email from Boehringer Ingelheim’s Jutta Heinrich-Nols to others at the firm:

“is it really wanted to publish this exposure-event paper of RELY ?

I cannot believe that for a decade a drug was developed with the clearly defined target of no monitoring needs, a prospective trial without plasma level monitoring was performed generating the RELY study results, that we promote 2 fixed doses without monitoring, defend continuously to Health Authorities that individual patient characteristics do not allow a dose titration based on plasma level only and then finally release a publication where exposure event relationships which was neither prospectively defined nor adequately conducted are described to define an effective and safe plasma level range....

This will make any defense of no monitoring to HA extremely difficult (i.e. Health Canada, TGA) and undermine our efforts to compete with other NOACs [new oral anticoagulants].
As I am not empowered [sic] to release or stop any publications I would like to ask you to check once again whether this is really wanted.”

Boehringer Ingelheim had made a deliberate decision to try to market Pradaxa without a counterpart to warfarin’s blood tests, according to a court filing. The judge wrote about “the decision to seek approval for Pradaxa prior to the development of a reversal agent and without a protocol for monitoring its therapeutic level.” He described that as a “critical” issue.

Another document filed with the court shows that the issue of blood tests for patients on Pradaxa came up when the company held a practice session in advance of its 2010 appearance before the FDA advisory committee.

“I’m trying to understand where in taking care of patients, it might be nice to have the information called the plasma concentration of your drug,” one participant in the mock question-and-answer session said, according to a transcript. The participant, Craig Pratt, added that he was “not trying to imply that everybody should have it done once a month,” but he observed that there is a “relationship between dose and plasma concentration. And there is a relationship between plasma concentration and bleeding risk, or risks,” the transcript says.

According to the transcript of the practice session, Boehringer Ingelheim’s Reilly explained that there were a number of situations in which “there’s a clear role” for monitoring and “you’d want to know.” A bedside test would be ideal, Reilly added, but “We don’t have that....”

(Interviewed by POGO, Pratt first said he would be shocked if he made the statement attributed to him in the transcript and then said he didn’t remember any specific question that he asked.)

Though the FDA approved Pradaxa without a monitoring system, an email cited by the judge shows that doctors who prescribe anticoagulants were not content with that state of affairs and that people within Boehringer Ingelheim were taking a fresh look at the issue. The May 2012 email was from Klaus Dugi (identified in a 2012 Boehringer Ingelheim news release as “Corporate Senior Vice President Medicine”) to the company’s top executive, Andreas Barner. Though the absence of warfarin-like testing with Pradaxa “is one of the most frequently stated advantages,” Dugi told Barner, according to the judge, “prescribers continue to express a need for additional tools or clinical markers to identify patients at high risk of bleed.”

In the email, Dugi proposed a strategy for monitoring blood plasma or anticoagulant activity, the judge wrote. Explaining the potential advantages of such a strategy, Dugi spoke in terms of safety and implied that there was significant room for improvement. According to the judge, Dugi hypothesized that the monitoring could lead to “a reduction of major bleeding events compared to well controlled warfarin of perhaps up to 30-40%.”

Drawing on data from the same clinical trial that won FDA approval for Pradaxa in 2010, a paper examining the plasma concentration issue was published in the February 2014 edition of the Journal of the American College of Cardiology. The paper, whose authors included Reilly, Lehr, and leaders of the RE-LY trial, concluded that ischemic stroke and bleeding outcomes “were correlated with dabigatran plasma concentrations.” And, for patients taking the drug, the concentrations of the drug in their system (“plasma concentrations”) showed “a more than 5-fold variation,” the paper said.
The paper appeared to validate a concern that Darren McGuire and other members of the FDA advisory committee considered before endorsing Pradaxa. At least implicitly, it appeared to call into question the FDA’s decision to approve the drug on what was essentially a one-size-fits-all basis.

“Individual benefit–risk might be improved,” the paper said, “by tailoring dabigatran dose after considering selected patient characteristics.”

Internal Boehringer Ingelheim documents show that people within the company have studied a fundamental shift in strategy for Pradaxa. A PowerPoint-style presentation laying out a proposal, marked “Confidential – Internal use only,” includes this summation:

“If data acceptable to regulators: Re-Launch Pradaxa with titration strategy (resulting in significantly fewer strokes and significantly fewer bleeding events compared to warfarin), Point of Care testing device and availability of Antidote.”

Neither the company nor the FDA has followed that strategy.

“The totality of scientific evidence does not support dosing decisions for Pradaxa® based solely on blood levels,” Boehringer Ingelheim said in a 2014 news release.

Epilogue: Years after approving Pradaxa, the FDA appears to be having some second thoughts about its approach to the drug.

In May 2014, Boehringer Ingelheim agreed to pay $650 million to settle lawsuits alleging Pradaxa had harmed patients. But the company stood by its drug, and, in its defense, it invoked the FDA.

“FDA has publicly stated that Pradaxa® 150 mg twice daily offers a positive benefit-risk profile and provides an important health benefit when used as directed…,” the company said in a news release.

The company also invoked the superiority claim that the FDA had originally denied the drug. “Compared to the 50 year-old anticoagulant warfarin, Pradaxa® 150 mg dose taken twice daily is superior at reducing the risk of ischemic and hemorrhagic strokes with a comparable rate of bleeding to the warfarin treatment.”

The drug maker reiterated one of its main selling points: that Pradaxa works “without the need for routine coagulation monitoring or dose adjustment.”

In a December 2014 slide presentation for European regulators, the FDA’s Robert Temple sent a strikingly different message, telegraphing that the FDA was reconsidering its approach to Pradaxa and other new generation oral anticoagulants.

“It is possible that if blood levels were not too variable a single dose”—in other words, the same dose for each patient—“could get most people into proper range,” Temple said. “We know that is not true for dabigatran …, he added.” (Emphasis in original)
Though people “like to avoid monitoring,” Temple added, “optimizing dose or blood level seems like a very good idea.”

On March 3, 2015, Boehringer Ingelheim announced that it had submitted for FDA review a new drug it had developed to reverse the effects of Pradaxa. The company said it was asking the FDA to approve the antidote on an accelerated basis.

On April 23, 2015, more than four years after the FDA approved Pradaxa, Boehringer Ingelheim announced that the FDA had agreed to give the reversal agent “Priority Review.” In FDA parlance, that meant the antidote had the potential to offer a “significant improvement” in safety or effectiveness.
Recommendations

The FDA needs to prioritize acting in the public interest rather than accommodating the drug industry. The FDA should exert its existing authority to solve many of the problems highlighted in this report. For example, it should require statistical manuals for clinical trials—the rules by which the results will be counted and scored—to be written before the data are gathered.

Some of the more detailed recommendations below would be difficult to implement under the current level of FDA funding, and therefore Congress should consider these needs when providing future funding.

1. The FDA should reject drug applications based on seriously flawed trials, including trials that ignore important FDA recommendations about how those trials should be conducted.

2. The FDA should use black box warnings to explain that trials that serve as the basis for FDA approval can have serious limitations as predictors of how drugs will perform in the population at large and that dangerous side effects may not be identified until the drugs have been widely prescribed over a period of years.

3. The FDA should require public financial disclosures of payments to and contracts with the academic research organizations and contract research organizations that manage clinical trials as well as clinical investigators who operate individual sites. Those disclosures would help illuminate any financial incentives to tilt trial results in favor of FDA approval. The FDA should require advisory committee members to file financial disclosures for several years after they serve on advisory committees. The FDA should make all advisory committee financial disclosures public.

4. The FDA should suspend or ban from clinical trials doctors who have repeatedly or egregiously violated standards for such trials. If past offenders are allowed to participate in new trials, the FDA should monitor their work or restrict their involvement for a probationary period.

5. The FDA should make sure that sponsors of clinical trials have timely, ready, one-stop access to potentially disqualifying information about doctors who might serve as clinical investigators in those trials. In addition to violations of clinical-trial standards, this database should include charges of professional misconduct by state medical boards, malpractice claims, and civil or criminal actions by state and federal law enforcement authorities. Sponsors of clinical trials should be required to review this information and provide justification if they choose doctors who have been cited for misconduct to participate in the trials.

6. The FDA should conduct more inspections of clinical investigators. In addition, FDA Establishment Inspection Reports and Form 483s documenting inspection results should be posted online. The drugs being tested and the clinical trials involved should be disclosed in the publicly posted forms and reports. These should be posted before an
advisory committee meets to discuss the drugs mentioned within the forms and reports, or, in the absence of an advisory committee hearing, before the FDA approves the drug.

7. The FDA should require clinical investigators to electronically submit each data point they collect within two days of the patient visit at which the data point was generated. The FDA or the National Institutes of Health should maintain a secure repository for such reporting. The real-time submission of the information to a government-controlled data bank would make it more difficult for researchers to fabricate clinical trial data and would help facilitate more efficient and effective FDA audits of clinical trial data.

8. The FDA should establish an entity free of financial conflicts of interest to handle trial randomization—the assignment of subjects to a control group or experimental treatment—so that the drug-maker sponsoring the clinical trial cannot know which subjects are taking the drug that is being tested and there is less opportunity for bias to skew the trial.

9. The FDA should modernize the FDA Adverse Event Reporting System (FAERS) to promote more thorough and consistent reporting of information that could help identify problems with drugs and other medical products.

10. The FDA should require that investigators and other contributors to clinical trials be publicly identified by full name, institutional affiliations, and practice address, to increase accountability.

11. The FDA should require drug companies to make public the patient-level data (stripped of personally identifiable information) gathered in clinical trials that serve as a basis for drug approvals. The information should be made public before FDA advisory committees convene to review the drugs, or, in the absence of an advisory committee hearing, before the FDA approves the drug.
Endnotes


2 Nellie Kay Denham, interview with John Crewdson, April 17, 2013.

3 Death Summary of Sidney Walter Denham.

4 Mary Denham, interview with John Crewdson, April 16, 2013.


6 Death Summary of Sidney Walter Denham.

7 Food and Drug Administration, “What does FDA do?”, http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194877.htm (Downloaded June 19, 2015)


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Case Management Order Number 50, p. 24.


Case Management Order Number 50, p. 24.

Dr. Jutta Heinrich-Nols, email message to Dr. Jeffrey Friedman, Dr. Martina Brueckmann, and Dr. Andreas Clemens, “WG: Exposure paper RELY,” February 4, 2013. http://www.pogoarchives.org/m/fda/heinrich_nols_email.pdf (Downloaded June 24, 2015) (Hereinafter Heinrich-Nols email “WG: Exposure paper RELY”)

Boehringer Ingelheim announces Pradaxa settlement.

2012 FDA Drug Safety Communication: Pradaxa:


David Madigan, interview with John Crewdson, November 18, 2013.


35 Dr. Steven E. Nissen, email message to John Crewdson; Transcript of Food and Drug Administration Center for Drug Evaluation and Research Cardiovascular and Renal Drugs Advisory Committee Hearing on Pradaxa, September 20, 2010, pp. 151-152. http://www.pogoarchives.org/m/fda/advisory_committee_transcript.pdf (Hereinafter Transcript of FDA Advisory Committee Hearing on Pradaxa)

36 Transcript of FDA Advisory Committee Hearing on Pradaxa, pp. 72-73.
37 Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 161.
38 FDA Clinical Review of Pradaxa, p. 18, Table 6; Transcript of FDA Advisory Committee Hearing on Pradaxa, pp. 218-219.
39 Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 162.


41 FDA Clinical Review of Pradaxa, pp. 58-60; Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 54.

42 Redacted Memorandum from Dr. Ellis F. Unger, Deputy Director of the Center for Drug Evaluation and Research, regarding “Deputy Office Director Decisional Memo,” October 19, 2010, p. 15. http://www.pogoarchives.org/m/fda/decision_memo_redacted.pdf (Hereinafter Redacted Deputy Office Director Decisional Memo Regarding Pradaxa)

43 Unredacted Memorandum from Dr. Ellis F. Unger, Deputy Director of the Center for Drug Evaluation and Research, regarding “Deputy Office Director Decisional Memo,” October 19, 2010. http://www.pogoarchives.org/m/fda/decision_memo_unredacted.pdf (Hereinafter Unredacted Deputy Office Director Decisional Memo Regarding Pradaxa)


46 Letter from Zarna Patel, Regulatory Review Officer, Office of Prescription Drug Promotion, to Nada Glavan, Associate Director, Drug Regulatory Affairs at Boehringer Ingelheim Pharmaceuticals Inc., about Pradaxa
http://www.pogoarchives.org/m/fda/misleading营销.pdf (Hereinafter Letter from Zarna Patel)

47 Memorandum from Sharon K. Gershon, p. 23.

48 Memorandum from Sharon K. Gershon, p. 3.

49 Warning letter from Leslie K. Ball, Director, Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research to Dr. Dov Linzer, regarding conduct of a clinical investigation, June 12, 2009.  
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm174744.htm (Downloaded September 8, 2015) (Hereinafter FDA Warning Letter to Dr. Dov Linzer)

50 FDA Warning Letter to Dr. Dov Linzer.

51 FDA Warning Letter to Dr. Dov Linzer.

52 FDA Warning Letter to Dr. Dov Linzer; Warning letter from Leslie K. Ball, Director, Division of Scientific Investigations, Office of Compliance, Center for Drug Evaluation and Research to Dr. Charles McKay, regarding conduct of a clinical investigation, October 23, 2009.  
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm188805.htm (Downloaded September 8, 2015) (Hereinafter FDA Warning Letter to Dr. Charles McKay)


Results of FDA inspections can be found in Food and Drug Administration, “Clinical Investigator Inspection Search.”  
http://www.accessdata.fda.gov/scripts/cder/cliil/index.cfm (Downloaded September 4, 2015) (Hereinafter “Clinical Investigator Inspection Search”)

54 “Clinical Investigator Inspection Search.”

55 Food and Drug Administration, “Inspections, Compliance, Enforcement, and Criminal Investigations: Part V- Regulatory/Administrative Strategy.”  
http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133571.htm (Downloaded September 8, 2015) (Hereinafter “Inspections, Compliance, Enforcement, and Criminal Investigations: Part V- Regulatory/Administrative Strategy”)

56 Food and Drug Administration, “Clinical Investigators - Disqualification Proceedings.”  

To put those numbers in perspective, there were more than 1,500 clinical investigators in the Pradaxa trial alone, and the site ClinicalTrials.gov, maintained by the National Institutes of Health, listed 199,046 studies as of September 23, 2015.

57 “RE-LY List and description of investigators and sites”; The number 170,784 can be found by subtracting the end of the 2004 number from the end of the 2014 number. National Institutes of Health,
ClinicalTrials.gov, “Trends, Charts, and Maps: Number of Registered Studies Over Time.”
https://clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime (Downloaded September 29, 2015)

Open Payments Data, “Darren McGuire.”

http://www.utsouthwestern.edu/facultydata/19303/files/McGuire%20CV_01_03_2014.pdf (Downloaded August 12, 2015) (Hereinafter Darren McGuire Curriculum vitae);
U.S. National Institutes of Health: ClinicalTrials.gov, “Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA),” August 4, 2015.
https://clinicaltrials.gov/ct2/show/NCT01897532?titles=carmelina&rank=1 (Downloaded August 12, 2015) (Hereinafter CARMELINA Clinical Trial)

60 UT Southwestern Medical Center, “Public Disclosures of Conflict of Interest.”
http://www.utsouthwestern.edu/research/research-administration/conflict-of-interest/faculty-conflicts.html (Downloaded August 17, 2015) (Requires a search for “McGuire”) (Hereinafter UT Southwestern Public Disclosures of Conflict of Interest)

61 Open Payments Data: Sanjay Kaul.

62 Boehringer Ingelheim Pharmaceuticals, Inc., “BIPI Dabigatran July 29th NYC Mock Q&A Session,” p. 58 of 98. (Hereinafter BIPI Dabigatran Mock Q&A Session)

63 3D Communications, “3D Communications Announces Formation of Cardiovascular Disease Advisory Board,” PRNewswire, April 23, 2013.

64 Tom Simon, telephone interview with Michael Smallberg, September 3, 2015.

http://www.pogoarchives.org/m/fda/judge_order_53.pdf (Hereinafter Case Management Order Number 53);


http://us.boehringer-

Dr. Gerald J. Dal Pan, interview with John Crewdson, July 3, 2013.

Dr. Ellis Unger, interview with John Crewdson and David Hilzenrath, June 14, 2013.

Transcript of FDA Advisory Committee Hearing on Pradaxa, pp. 66-67, p. 70.


Memorandum from Dr. Stephen M. Grant, Deputy Director of the Office of Drug Evaluation I - Division of Cardiovascular and Renal Products, regarding “Deputy Division Director Decisional Memo,” November 4, 2011. [Downloaded September 1, 2015] (Hereinafter Deputy Division Director Decisional Memo Regarding Xarelto)


FDA Clinical Review of Xarelto, p. 12.

Deputy Division Director Decisional Memo Regarding Xarelto, p. 3.

Deputy Division Director Decisional Memo Regarding Xarelto, p. 4.

Deputy Division Director Decisional Memo Regarding Xarelto, p. 8.


FDA Clinical Review of Pradaxa, p. 16.

94 The absence of an antidote does not mean that patients who hemorrhage while taking Pradaxa inevitably bleed to death. Counterintuitively, during the manufacturer-sponsored clinical trial that served as the basis for Pradaxa’s approval by the FDA, patients on warfarin who suffered major bleeds were more likely to die from them than patients on Pradaxa who experienced similar hemorrhages. According to a package of information the FDA prepared as part of its review of Pradaxa, in the clinical trial, 486 patients on the 150 mg dose of dabigatran suffered adjudicated major bleeds. Of those, 28 patients, or 5.8 percent, died. Meanwhile, 476 patients on warfarin suffered...
adjudicated major bleeds. Of those, 40 patients, or 8.4 percent, died. [FDA Clinical Review of Pradaxa](https://www.accessdata.fda.gov/drugsatfda_docs/npa/2014/022322s000 formas/022322briefsummary.pdf), pp. 117-118, Tables 73 and 74.

Data compiled from FDA adverse event reports present a different pattern. According to ISMP, in 2012, 17.7 percent of adverse events involving Pradaxa ended in death, compared with 6.5 percent of adverse events involving warfarin. [QuarterWatch: Leading Drug Safety Issues of 2012](https://www.quarterwatch.com/article.cfm?issueid=157), p. 10.


Dr. Ellis F. Unger, “Atrial fibrillation and new oral anticoagulant drugs.” [http://www.fda.gov/Drugs/NewsEvents/ucm405148.htm](http://www.fda.gov/Drugs/NewsEvents/ucm405148.htm) (Downloaded September 1, 2015) (Hereinafter “Atrial fibrillation and new oral anticoagulant drugs”)

[Atrial fibrillation and new oral anticoagulant drugs](http://www.fda.gov/Drugs/NewsEvents/ucm405148.htm); Kimberly Rawlings, email message to David Hilzenrath, September 21, 2015.

Dr. Robert Temple, Dr. Gerald J. Dal Pan, and Dr. Ellis Unger, interview with John Crewdson and David Hilzenrath, June 14, 2013;

Dr. Robert Temple, Dr. Gerald J. Dal Pan, and Dr. Ellis Unger, interview with John Crewdson, July 3, 2013.

[Redacted Deputy Office Director Decisional Memo Regarding Pradaxa](https://www.accessdata.fda.gov/drugsatfda_docs/npa/2014/022322s000 formas/022322briefsummary.pdf), pp. 9-11, p. 15.

Transcript of FDA Advisory Committee Hearing on Pradaxa.

[Redacted Deputy Office Director Decisional Memo Regarding Pradaxa](https://www.accessdata.fda.gov/drugsatfda_docs/npa/2014/022322s000 formas/022322briefsummary.pdf).

Dr. Sanjay Kaul to John Crewdson.

Dr. Steven E. Nissen, email message to David Hilzenrath, August 18, 2015.

Dr. Steven E. Nissen, email message to John Crewdson.

Dr. Steven E. Nissen, email message to John Crewdson.


Dr. Suzanne White Junod, Food and Drug Administration, “FDA and Clinical Drug Trials: A Short History.” [http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm#_ednref38](http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm#_ednref38) (Downloaded June 30, 2015)

Dr. Steven E. Nissen, interview with John Crewdson.
Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 119.

FDA Clinical Review of Pradaxa, p. 48; Transcript of FDA Advisory Committee Hearing on Pradaxa, pp. 117-119.

Transcript of FDA Advisory Committee Hearing on Pradaxa, pp. 151-152.

Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 218.


Memorandum from Sharon K. Gershon

FDA Clinical Review of Pradaxa, p. 9.

FDA Clinical Review of Pradaxa, p. 18.

Transcript of FDA Advisory Committee Hearing on Pradaxa, pp. 218-219.

Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 119.


Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 72.

Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 151.

Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 152.


Transcript of FDA Advisory Committee Hearing on Pradaxa, pp. 46-47; Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 30.

More than merely benefitting Pradaxa in the comparison, the way the lines were drawn might have tipped or come close to tipping the balance in favor of Pradaxa around an important statistical threshold. The FDA review zeroed in on an analysis of “all-cause mortality”—in other words, patient deaths. It said that “including deaths censored by the sponsor’s statistical analysis plan” shifted a measure called the p-value higher, to 0.06 from 0.052. (FDA Clinical Review, p. 48.)

The p-value is a measure of statistical significance, and 0.05 is generally regarded as the upper limit for statistical significance. Therefore, the FDA staff review was essentially saying that counting certain deaths that the statistical analysis plan excluded could have rendered statistically insignificant a point that otherwise just barely favored Pradaxa.

The FDA review included a related discussion. “Following database lock, two additional deaths were identified; one in the dabigatran 110 arm and one in the dabigatran 150 arm. In addition to these deaths, ten other deaths (six in the dabigatran 150 mg arm and four in the warfarin arm) were reported by investigators but were excluded from key analyses based on rules specified by the sponsor’s statistical analysis plan…. Conducting the analysis according to the finalized statistical analysis plan gives a p-value of 0.052 for the 150 dose; inclusion of the ten deaths described above shifts the p-value to 0.060.” (FDA Clinical Review, pp. 58-60.)

P-values explained: “If it is to be shown that a new drug is better than an old one, the first step is to show that the two drugs are not equivalent. Thus, the hypothesis of equality is to be rejected. The null hypothesis (H0) to be rejected is then formulated in this case as follows: ‘There is no difference between the two treatments with respect to their effect.’ For example, there might be no difference between two antihypertensives with respect to their ability to reduce blood pressure. The alternative hypothesis (H1) then states that there is a difference between the two treatments…. To permit a decision between the null hypothesis and the alternative hypothesis, significance limits are often specified in advance, at a level of significance α. The level of significance of 0.05 (or 5%) is often chosen. If the p-value is less than this limit, the result is significant and it is agreed that the null hypothesis should be rejected and the alternative hypothesis—that there is a difference—is accepted.” (Emphasis added)
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2689604/ (Downloaded September 15, 2015)

140 Transcript of FDA Advisory Committee Hearing on Pradaxa, pp. 106-107.  
141 FDA Clinical Review of Pradaxa, p. 18.  
143 Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 160.  
144 Redacted Deputy Office Director Decisional Memo Regarding Pradaxa, p. 15.  
145 “Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran”:  
“Supplementary Appendix to Dabigatran versus Warfarin in Patients with Atrial Fibrillation”;  
146 David Kessler, email to Lydia Dennett, September 11, 2015.  
FDA Clinical Review of Pradaxa, p. 44.  
http://apps.elsevier.es/watermark/ctl_servlet?_f=10&pident_articulo=13181508&pident_usuario=0&pcontactid=&pident_revista=600&tv=144&accion=L&origen=zonadelectura&web=www.elsevier.es&lan=en&fichero=600v376n9745a13181508pdf001.pdf (Downloaded July 13, 2015)  
149 FDA Clinical Review of Pradaxa, p. 40.  
150 Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 155, p. 222.  
151 Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 107.  
152 Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 111.  
153 Transcript of FDA Advisory Committee Hearing on Pradaxa, pp. 112-114.  
155 Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 124.  
156 Redacted Deputy Office Director Decisional Memo Regarding Pradaxa, p. 15.
157 Redacted Deputy Office Director Decisional Memo Regarding Pradaxa, p. 15.

158 Redacted Deputy Office Director Decisional Memo Regarding Pradaxa, p. 15.

159 Food and Drug Administration, “Regulatory Information: FOI Information,”
http://www.fda.gov/RegulatoryInformation/FOI/ucm390370.htm (Downloaded July 14, 2015)

160 Unredacted Deputy Office Director Decisional Memo Regarding Pradaxa.

161 As of September 28, 2015, the redacted version of the Unger memo was still posted on the FDA website at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000SumR.pdf.

162 Minutes for the September 20, 2010, Meeting of the Cardiovascular and Renal Drugs Advisory Committee.

163 “Regulatory Project Manager Overview,”

164 Memorandum from Dr. Aliza Thompson, Medical Officer, to file, regarding “Dabigatran (NDA 22-512) and labeling pertaining to efficacy,” May 25, 2012, pp. 2-3.
http://www.pogoarchives.org/m/fda/2012_labeling_memo.pdf

165 “Regulatory Project Manager Overview,” p. 2.

166 Deposition of Dr. Andreas Clemens, pp. 74-75.

167 Letter from Zarna Patel; Pradaxa.com, December 27, 2011.

168 Letter from Zarna Patel.

169 Letter from Zarna Patel.

170 Letter from Zarna Patel.

171 “Dabigatran versus Warfarin in Patients with Atrial Fibrillation.”

172 Memorandum from Sharon K. Gershon, p. 3.

173 Memorandum from Sharon K. Gershon, p. 3.


175 Memorandum from Sharon K. Gershon, p. 5.


177 FDA Clinical Review of Pradaxa, p. 21, p. 26 Table 8.
Memorandum from Sharon K. Gershon, p. 5.

Memorandum from Sharon K. Gershon, p. 4.


“Additional Events in the RE-LY Trial.”


The FDA conducted these inspections in some form of collaboration with the EMA, its European counterpart, according to the Gershon memo. The division of labor is not explained. Memorandum from Sharon K. Gershon, p. 6.


The FDA’s authority and options are described in the following provisions:


FDA enforcement is described in these resources:

Food and Drug Administration, “FDA Compliance and Enforcement Information.” http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm254426.htm (Downloaded September 8, 2015);

Food and Drug Administration, “Warning and Untitled Letters.” http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm284105.htm (Downloaded September 8, 2015);

“Clinical Investigators - Disqualification Proceedings.”

For instance, 21 U.S.C. § 331(e) prohibits the “failure to establish or maintain any record, or make any report, required under” 21 U.S.C. § 355(i), the provision that governs research by investigators in clinical trials. Under 21 U.S.C. § 333, a person who violates “a provision of section 331 … shall be imprisoned for not more than one year or fined not more than $1,000, or both.” If the person commits this violation “with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $10,000, or both.” 21 U.S.C. § 333; Prohibited acts, 21 U.S.C. § 331(e). http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapIII-sec333.pdf (Downloaded September 8, 2015);


Memorandum from Sharon K. Gershon, p. 25.

Memorandum from Sharon K. Gershon, p. 25;

FDA Clinical Review of Pradaxa, p. 22.

Memorandum from Sharon K. Gershon, p. 25.

FDA Warning Letter to Dr. Dov Linzer;


Department of Health and Human Services, Food and Drug Administration, “Form FDA 483 to Dov Linzer, MD, Principal Investigator Study Protocol No. 1160.26 (RE-LY),” December 15, 2008.

FDA Warning Letter to Dr. Dov Linzer.

FDA Warning Letter to Dr. Dov Linzer.

FDA Warning Letter to Dr. Dov Linzer.

FDA Warning Letter to Dr. Dov Linzer.
“Clinical Investigator Inspection Search.” (Requires a search for “Linzer”)

Food and Drug Administration, “Clinical Investigator Inspection List (CIIL) Database Codes: Database Code Definitions.”
http://www.fda.gov/Drugs/GuidanceCompliance RegulatoryInformation/EnforcementActivitiesbyFDA/ucm073059.htm (Downloaded September 8, 2015) (Hereinafter “Clinical Investigator Inspection List (CIIL) Database Codes: Database Code Definitions”)  

“Clinical Investigators - Disqualification Proceedings.”

Letter from Dov Linzer, M.D., to Tejashri Purohit-Sheth, M.D., and Leslie K. Ball, M.D., Division of Scientific Investigation, Office of Compliance, Center for Drug Evaluation and Research, Food and Drug Administration, regarding warning letter, July 10, 2009.

Dr. Dov Linzer, interview with John Crewdson, May 2, 2013.

“Supplementary Appendix to Dabigatran versus Warfarin in Patients with Atrial Fibrillation.”

FDA Warning Letter to Dr. Charles McKay;
Harbor-UCLA Medical Center: Division of Cardiology, “Harbor-UCLA Faculty.”
http://cardiology.labiomed.org/harbor-ucla-faculty/ (Downloaded September 8, 2015)

The warning letter does not name the RE-LY trial. However, a master list of principal investigators in the RE-LY trial identifies McKay as responsible for site number 276. The FDA Clinical Review (Table 9) identifies site 276 as one of those “closed for cause” by Boehringer Ingelheim and notes that a warning letter was issued. In addition, though the name of the clinical trial is redacted in an FDA Establishment Inspection Report for McKay obtained by POGO, the body of the document mentions dabigatran.

FDA Warning Letter to Dr. Charles McKay;
“RE-LY List and description of investigators and sites”;
FDA Clinical Review of Pradaxa, p. 22, Table 9;


FDA Clinical Review, “Table 9: Sites closed for cause by sponsor,” says data from sites 265 and 276 “should not be used to support application.” The master list of RE-LY principal investigators identifies Linzer and McKay as responsible for those sites, respectively.

FDA Clinical Review of Pradaxa, p. 22, Table 9;
“RE-LY List and description of investigators and sites.”

Memorandum from Sharon K. Gershon, p. 12.

“Supplementary Appendix to Dabigatran versus Warfarin in Patients with Atrial Fibrillation,” p. 6.

“Over 20,000 patients were screened and 18,113 were randomized.” In other words, for the trial as a whole, at least 9.4 percent of those screened were not enrolled. Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 14.

Memorandum from Sharon K. Gershon, p. 12.

Memorandum from Sharon K. Gershon, p. 12.
The results of the RE-LY trial were published in *The New England Journal of Medicine* more than a year earlier—in September 2009. “Dabigatran versus Warfarin in Patients with Atrial Fibrillation.”

“Clinical Investigators - Disqualification Proceedings.”

“Clinical Investigator Inspection Search.” (Requires a search for “Nana”)

“Clinical Investigator Inspection List (CIIL) Database Codes: Database Code Definitions.”

Dr. Maria Anastasiou-Nana, telephone call with Dimitrios Manis, August 2015.

Memorandum from Sharon K. Gershon, pp. 12-14; “Whether or not there were additional events that were not reported by investigators is an issue that the DSI audits will address,” the FDA Clinical Review says. (Emphasis in original) FDA Clinical Review of Pradaxa, p. 22.

Transcript of FDA Advisory Committee Hearing on Pradaxa, p. 276.

“FDA approves Pradaxa to prevent stroke in people with atrial fibrillation”;

In the August 2010 report, the reviewers mention taking into account inspection results. They also mention that more were expected:

“Reviewer’s comment: The inspections have not yet been completed; however at this time, results of DSI audits suggest that there was compliance with good clinical practices and the trials were conducted in accordance with accepted ethical standards…

“whether or not there were additional events that were not reported by investigators is an issue that the DSI audits, some still pending, will address.” (Emphasis in original) FDA Clinical Review of Pradaxa, p. 24, pp. 47-48.


FDA Warning Letter to Raymond E. Tidman.

FDA Warning Letter to Raymond E. Tidman.

Letter from Raymond E. Tidman, MD, to Leslie K. Ball, Branch Chief, Division of Scientific Investigations, Office of Medical Policy, Center for Drug Evaluation and Research, responding to warning letter,

From Federal Register notice of final rule:

“The interpretations of the terms ‘repeatedly’ and ‘deliberately’ in FDA’s regulations governing disqualification of clinical investigators are well established. The term ‘repeatedly’ means, simply, more than once. A violation occurs ‘repeatedly’ if it happens more than once.

“FDA may consider disqualification if a clinical investigator commits a regulatory violation more than one time within a single study (e.g., enrolling in a single study two study subjects who were ineligible because of concomitant illnesses that put those subjects at greater risk) or one time in each of two studies (e.g., enrolling in each of two studies, a study subject who was ineligible because of a concomitant illness putting the subject at greater risk). The Commissioner, in past decisions, has determined that multiple violations within a single study constitute repeated violations sufficient to support disqualification from receipt of test articles.

“The term ‘deliberately’ includes conduct that is ‘willful’ as well as conduct demonstrating reckless disregard. Accordingly, when a clinical investigator knowingly fails to comply with FDA’s regulations, the clinical investigator may be found to have deliberately violated the regulations. FDA could pursue the disqualification of a clinical investigator, for example, if the investigator changed a study’s results by altering a data field on a case report form to include false data. Likewise, an investigator who shows a reckless disregard for whether his or her conduct may result in a regulatory violation may be found to have deliberately violated the regulations.

“Decision makers in part 16 proceedings have interpreted the term ‘deliberately’ in § 312.70(b) as roughly synonymous with the ‘deliberate indifference’ or ‘willful’ standard of intent. This standard does not require specific knowledge that behavior, such as submission of false data to a study sponsor, violates the law, but reckless disregard for what the regulations require. The Commissioner’s decision In the Matter of Layne O. Gentry provides a useful discussion of the standard for ‘deliberate’ behavior in a disqualification proceeding:

*** the term ‘deliberate,’ when used to describe a category of violations that might lead to legal consequences, does not necessarily require a showing of subjective intent on the part of the person in question.

*** the purpose of [disqualification] is to protect the safety of patients and to preserve the integrity of the data needed to assess the safety and effectiveness of drugs before being sold to the general public through disqualifying investigators who do not fulfill the responsibilities imposed on them.

“In the context of such a remedial, as opposed to punitive, scheme, an objective standard for ‘deliberate’ or ‘deliberately’ is a better fit because the inquiry should focus on preventing risk rather than imposing punishment for culpable conduct. Even if the investigator did not intend for the violations to occur, conduct demonstrating a reckless disregard for the regulatory requirements calls into question the investigator’s fitness for conducting clinical trials.

“Inspections, Compliance, Enforcement, and Criminal Investigations: Part V- Regulatory/Administrative Strategy.”

“Clinical Investigator Inspection Search.” (Requires a search for “Bellinger”)


“Clinical Investigator Inspection Search.” (Requires a search for “Hack”);
“Clinical Investigator Inspection List (CIIL) Database Codes: Database Code Definitions.”

“Supplementary Appendix to Dabigatran versus Warfarin in Patients with Atrial Fibrillation.”

https://circ.ahajournals.org/content/suppl/2013/09/09/CIRCULATIONAHA.112.000491.DC1/000491_supplemental_material.pdf;

Jack Hirsh, telephone interview with David Hilzenrath, July 7, 2015.

“Clinical Investigator Inspection Search.” (Requires a search for “Hirsh”)

Jack Hirsh, email to David Hilzenrath, “Re: Follow-up question,” July 8, 2015; Jack Hirsh, telephone interview with David Hilzenrath, July 7, 2015.

Consent Order, In the Matter of Terrence C. Hack, M.D., Commonwealth of Massachusetts, Board of Registration in Medicine, Adjudicatory Case No. 2006-050, September 20, 2006, p. 22 of pdf. (Hereinafter Hack Consent Order)

Hack Consent Order, p. 23 of pdf.

Hack Consent Order, p. 25 of pdf.

Stipulation for Public Reprimand, In the Matter of the Accusation Against Terrence C. Hack, M.D., before the Division of Medical Quality, Medical Board of California, Department of Consumer Affairs, State of California, Case No. 16-2006-178671, May 8, 2007, pp. 4-7 of pdf, p. 11 of pdf.


Memorandum from Sharon K. Gershon, p. 25;
“RE-LY List and description of investigators and sites.”


Food and Drug Administration, “Clinical Investigators - Disqualification Proceedings – Detail.” 
“Clinical Investigator Inspection Search.” (Requires a search for “Morcos”); “Establishment Inspection Report: Nabil Charle Morcos, M.D., PhD”; Department of Health and Human Services, Food and Drug Administration, “Form FDA 483 to Nabil Charle Morcos, M.D., PhD, Principal Investigator,” April 15, 2010.


“Dabigatran versus Warfarin in Patients with Atrial Fibrillation.”

Memorandum from Sharon K. Gershon, p. 25.

Food and Drug Administration, “Clinical Investigator Inspection List (CIIL).” http://www.fda.gov/Drugs/InformationOnDrugs/ucm135198.htm (Downloaded July 21, 2015) (Hereinafter “Clinical Investigator Inspection List (CIIL)”)

“Clinical Investigator Inspection Search”: “RE-LY List and description of investigators and sites.”

“RE-LY List and description of investigators and sites.”

“Clinical Investigator Inspection List (CIIL) Database Codes: Database Code Definitions.”

“Clinical Investigator Inspection Search.”

“Clinical Investigator Inspection Search.”

“Clinical Investigator Inspection Search.”

“Inspections, Compliance, Enforcement, and Criminal Investigations: Part V - Regulatory/Administrative Strategy.”


From 2005 through 2014, the FDA issued 59 orders debarring individuals from working for anyone with an approved or pending drug approval application, according to notices published in the Federal Register and posted on the FDA’s website. In some cases, investigators have been debarred for alleged violations in clinical trials, such as falsifying study participant data. But that’s not all: the FDA also has the authority to debar individuals who are convicted of other types of violations, such as bribery or illegally prescribing medications. Food and Drug Administration, “FDA Debarment List (Drug Product Applications),” updated July 28, 2015. http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/ucm139627.htm (Downloaded September 15, 2015); 21 U.S.C. § 335(a).

Elizabeth Woeckner, email to John Crewdson, August 29, 2013.
Elizabeth Woeckner, email to John Crewdson, August 26, 2013; Elizabeth Woeckner, telephone interview with Michael Smallberg, August 19, 2015.

“Clinical Investigator Inspection List (CIIL).”


“Supplementary Appendix to Dabigatran versus Warfarin in Patients with Atrial Fibrillation.”

“Adverse Events Custom Report – Final.”


“Acutely Injured Patients on Dabigatran,” p. 2.

“Acutely Injured Patients on Dabigatran,” p. 2.


Dr. Gerald J. Dal Pan, interview with John Crewdson, July 3, 2013.


2012 FDA Drug Safety Communication: Pradaxa


“Dabigatran and Postmarketing Reports of Bleeding.”


“Dabigatran and Postmarketing Reports of Bleeding,” p. 1273.


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