

CONFLICTS OF INTEREST IN THE DRUG INDUSTRY'S RELATIONSHIP WITH THE GOVERNMENT

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I. INTRODUCTION

In a 2004 essay for the Hastings Center, University of Minnesota bioethicist Carl Elliott gave a witty account of how academic and government scientists who get money from the pharmaceutical industry assure the public that those financial ties have no influence on their behavior: "The degree of dissembling and rationalization here might be funny if the stakes were not high."¹ He continued:

"I take the money but it doesn't influence me." "I take the money from many different sources in order to keep my objectivity." "I take the money but I make sure that no more than forty percent of our center's funding comes from corporate sources." "I take the money but I always disclose." "I take the money but I say what I want." Or my favorite: "I take the money but I use it to advocate for social justice." The rationalizations always begin with the phrase: "I take the money." No one will just say no.²

Actually, many physicians and scientists involved in health care do say no, and they represent a vastly underutilized resource when it comes to ending the conflicts of interest arising from the drug industry's relationship with the government. But before I get to solutions to this problem, allow me to outline why I believe this is a problem of the first-order magnitude—one that must be resolved if we are going to restore the public's faith in the integrity of the government's drug oversight system.

And make no mistake about it—in the wake of the Vioxx scandal, which resulted in the unnecessary deaths of tens of thousands of Americans, the public's faith in the Food and Drug Administration is definitely shaken. According to a Harris Poll taken in May 2006, only thirty-six percent of the public thought the FDA was doing a "good" or "excellent" job with respect to its oversight of drug safety and efficacy,

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1. Carl Elliott, *Pharma Goes to the Laundry: Public Relations and the Business of Medical Education*, HASTINGS CENTER REP., Sept.-Oct. 2004, at 18, 22.

2. *Id.*

while fifty-eight percent thought it was doing a “fair” or “poor” job.³ Just two years earlier, the response was just the opposite: fifty-six percent thought the agency’s performance in this area was good or excellent while only thirty-seven percent thought it was fair or poor.⁴

Lest you think this sharp slide in public opinion is entirely attributable to the publicity that surrounded Merck’s travails with Vioxx, there were other questions in the poll suggesting that the public’s concerns about industry influence over the FDA go much deeper than just safety. Over sixty percent of the public in this poll negatively viewed the agency’s function of hastening the market entry of low-cost generics.⁵ Only twenty-one percent of those surveyed, however, believed the agency’s primary function was to bring innovative medicines to market,⁶ which is industry’s primary concern. Compare this to the fifty-eight percent whose number one fear was drug safety.⁷ Yet, that public rejection of the industry’s primary issue is not a recent concern. Safety also trumped innovation as a concern by a fifty-four to twenty-three margin two years prior to this survey, before Vioxx hit the headlines.⁸

II. THE FDA: A TROUBLED AGENCY

Why has an agency once thought of as the “gold standard” among federal regulatory agencies fallen on hard times? The economics literature has a phrase that describes the underlying phenomenon—it is called industry capture. A quarter century into the anti-regulatory backlash that began in the late 1970s and took off when Ronald Reagan entered office, it is fair to say that the nation’s food and drug watchdog has been qualitatively transformed. Today, it is an under funded lapdog.

The agency’s primary concern—by a statute passed in 1992—is expediting the review of new drug and device applications. This focus is mandated in the Prescription Drug User Fee Act of 1992 (“PDUFA”)⁹ and the companion Medical Device User Fee and Modernization Act of

3. *The FDA’s Reputation with the General Public Is Under Assault*, WALL ST. J. ONLINE/HARRIS INTERACTIVE HEALTH-CARE POLL (Harris Interactive Inc., Rochester, N.Y., May 26, 2006), at 4 tbl.2A, available at http://www.harrisinteractive.com/news/newsletters/wshealthnews/WSJOnline_HI_Health-CarePoll2006vol5_iss09.pdf (classifying “excellent” and “good” as “positive responses” and “fair” and “poor” as “negative” responses).

4. *Id.*

5. *See id.* at 1.

6. *Id.*

7. *See id.* at 2.

8. *Id.* at 5.

9. Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, §§ 101(a), 102(3), 106 Stat. 4491 (codified as amended at 21 U.S.C. § 379g note (2000)).

2002 ("MDUFMA").¹⁰ User fees today account for one-fifth of all agency funds.¹¹ But they command a disproportionate share of agency resources because the agency is required to match the user fees with comparable discretionary resources. The result: In 2005, the agency had 2395 full-time staff dedicated to evaluating new drug applications,¹² around 150% of the level in 1995.¹³ Moreover, the law quite specifically spells out how the use of industry funds should be measured. Every performance measure has to do with shortening the time it takes to approve a new drug application.¹⁴

The result is that virtually every other function of the agency has been systematically starved of the resources needed to carry out its mandates. Take drug safety, for example. The Institute of Medicine's thorough-going critique of the FDA's drug safety system, which was released in September 2006, points out that PDUFA's first two iterations, which must be reauthorized every five years, specifically proscribed the allocation of user fees for drug safety work. The third iteration, up for its fourth renewal this year, allowed the use of these fees for drug safety under very limited conditions—just post-marketing surveillance for the first two or three years a drug is on the market. Today, the entire Office of Drug Safety, which has primary responsibility for post-approval drug safety monitoring, has just ninety people. The FDA likes to point out that it has 700 people working on safety, but the vast majority of those staffers are working on pre-marketing Phase I safety reviews on new drugs, not post-marketing surveillance.

Drug safety is not the only part of the FDA starved for resources.

10. Medical Device User Fee and Modernization Act of 2002, Pub. L. No. 107-250, 116 Stat. 1588, 1589 § 101(3) (codified as amended at 21 U.S.C. § 379i note (2006)). MDUFMA was enacted to authorize fees that would be "dedicated to meeting the goals identified in the letters from the Secretary of Health and Human Services to the Committee on Energy and Commerce of the House of Representatives and the Committee on Health, Education, Labor, and Pensions of the Senate, as set forth in the Congressional Record." *Id.* Defraying the FDA's costs in "expediting review of device applications" was included among these goals. H.R. REP. No. 107-728, pt. 2, at 4 (2002).

11. Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Act, Pub. L. No. 109-97, 119 Stat. 2120, 2147-48 (codified in scattered sections of 7 U.S.C. 2006)) (appropriating \$1,838,567,000 to the FDA for fiscal year 2006, with \$356,950,000 originating from, among other user fees, PDUFA and MDUFMA).

12. FDA, Detail of Full-Time Equivalent (FTE) Employment Program Level, <http://www.fda.gov/oc/oms/ofm/budget/2006/HTML/Tables/DetailFTEEmp.htm> (last visited Feb. 21, 2007).

13. Daniel Carpenter et al., *Approval Times for New Drugs: Does the Source of Funding for FDA Staff Matter?*, HEALTH AFF., Dec. 17, 2003, at W3-621 exhibit 1, <http://content.healthaffairs.org/cgi/reprint/hlthaff.w3.618v1.pdf> ("web exclusive").

14. INST. OF MED. OF THE NAT'L ACADS., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 153-62 (Alicia Baciú et al. eds., 2006).

The recent spinach E. coli outbreak has brought the issue of food safety once again before the public. In the wake of 9/11, Congress appropriated additional funds to beef up food safety inspections, especially for the growing proportion of our food that comes from abroad.¹⁵ And 200 staff members were added to that department. Yet, since 2003, the FDA's Center for Food Safety and Nutrition budget has been cut by twenty-seven percent and staffing reduced by fourteen percent. Staffing is now below pre-9/11 levels.¹⁶

The other inspection divisions of the agency are also a pale shadow of their former selves. Inspections of domestic and overseas drug manufacturing plants and the policing of false claims in advertising, especially in the unregulated supplements market, but also for regulated drugs, are down across the board. According to a report issued by the Democratic minority in the House Government Reform Committee last June, FDA warning letters fell fifty percent between 2000 and 2005.¹⁷

The user fee acts are a structural conflict of interest that must be resolved if the agency is going to once again become the gold standard for federal regulatory agencies. Even if Congress were to substantially increase the agency's discretionary funds, if it does not simultaneously end or restructure the user fee system, the scientists in the Center for Drug Evaluation and Research will remain subject to the subtle pressures formed when their job security is tied up in maintaining a friendly environment for the companies they are regulating.

Strong leadership at the FDA could have mitigated some of the pressures created by the structural conflict of interest arising out of the user fee acts. Under President Clinton, FDA commissioner David Kessler did an admirable job going after the tobacco companies, but left the pharmaceutical industry pretty much alone.¹⁸ The result: New records were set for new drug approvals during his tenure. But new records were also set for drug withdrawals as a slew of unsafe drugs hit the market.¹⁹ In this decade, under President George W. Bush, the

15. See Public Health Security and Bioterrorism Preparedness and Response Act of 2002, Pub. L. No. 107-188, §§ 301-302, 116 Stat. 594, 662-63 (codified as amended at 21 U.S.C. § 341 note (2006)).

16. Press Release, Statement of CSPI Executive Director Michael Jacobson, Ctr. for Sci. in the Pub. Interest, Coalition for a Stronger FDA Says Agency Needs More Resources (Sept. 25, 2006), <http://www.cspinet.org/new/200609251.html>.

17. COMM. ON GOV'T REFORM—MINORITY STAFF, U.S. HOUSE OF REPRESENTATIVES, PRESCRIPTION FOR HARM: THE DECLINE IN FDA ENFORCEMENT ACTIVITY 7 (2006), available at <http://www.democrats.reform.house.gov/Documents/20060627101434-98349.pdf>.

18. See Marian Burros, *F.D.A. Commissioner Is Resigning After 6 Stormy Years in Office*, N.Y. TIMES, Nov. 26, 1996, at A1.

19. See Sabin Russell, *FDA Lax in Drug Safety, Journal Warns*, S.F. CHRON., Nov. 23, 2004, at A1 (noting that drug recalls rose to 5.4% during 1997-2001, up from 1.6% in the previous four

agency has largely operated in a leadership vacuum. The previous commissioner, Lester Crawford, resigned because of a conflict of interest scandal.²⁰ And the new commissioner, cancer surgeon Andrew von Eschenbach, came to the FDA after several years atop the National Cancer Institute ("NCI").

Dr. von Eschenbach's tenure represents another structural conflict of interest. NCI and the broader National Institutes of Health ("NIH"), of which it is a part, are the public sector's health care research and development departments. Their mission is to investigate the causes and, more importantly, come up with cures for disease. An internal study conducted a decade ago found that NCI developed, almost entirely on its own, eighty percent of the first fifty-nine cancer chemotherapy drugs. It runs a nationwide network of clinical trial centers—the Cancer Oncology Groups—that remain the backbone for testing new cancer drugs for government and industry alike. As head of NCI, Dr. von Eschenbach was a forceful advocate for "eliminating death and suffering from cancer by 2015."²¹ He believes the exponential growth of genetic information about cancer has created the intellectual foundation for finally conquering this dreaded disease, and he sees it as his mission to more rapidly facilitate the creation of new tools, diagnostics and therapies based on this knowledge. I have no problem with Dr. von Eschenbach's advocacy, although as David Willman's reporting at the *Los Angeles Times* has shown, numerous scientists at NIH, including at NCI, went overboard in building relationships with industry, to the point where their conflicts of interest actually got in the way of developing effective therapeutics.²² I believe in government-industry collaboration in research and development. But as the head of NCI or any agency at NIH, it is one's job to ensure that agency scientists collaborate in an evenhanded way with all industry comers. Alternatively, one must not let individual conflicts of interest stand in the way of broad dissemination of knowledge generated with taxpayer funds. In short, helping scientists—whether they are in government or industry—to develop cures for disease is the agency head's job. It is not part of that job to sign special deals with specific firms for personal financial gain.

Unfortunately, Dr. von Eschenbach has brought the same mindset

years).

20. In October 2006, Lester Crawford pleaded guilty to charges that he owned stock in firms regulated by the FDA while he was commissioner. *Ex-head of Food Agency Pleads Guilty of Lying*, INT'L HERALD TRIB., Oct. 18, 2006, at 8.

21. Matthew Chayes, *Cancer Cure Goal Praised, Criticized*, CHI. TRIB., Apr. 8, 2006, at C3.

22. David Willman, *Stealth Merger: Drug Companies and Government Medical Research*, L.A. TIMES, Dec. 7, 2003, at A1.

to the FDA, which fundamentally confuses the purposes of the two agencies. The FDA's job is to ensure that applicants prove that their new drugs are, number one, safe, and number two, effective. In enforcing those standards over time, the FDA has proved a valuable handmaiden for industry, in effect teaching it how to do its job and creating a level playing field for industry competition. But its essence is to be the arbiter of safety and efficacy, to wear green eyeshades, so to speak. To put a cheerleader for new cures based on still largely unproven theories about genetically targeted therapies atop the agency is to fundamentally misunderstand what the FDA is supposed to be about. That the Bush Administration then appointed Scott Gottlieb, a thirty-three year old physician, who moonlighted as a drug industry stock analyst for a Wall Street newsletter, as deputy commissioner simply compounded the error and the functional confusion that has characterized the leadership of the agency for most of this decade.

III. INDUSTRY INFLUENCE ON RESEARCH

Of course, the outside academic and clinical medicine communities could have served as a brake on the tendencies fostered by these conflicts of interest. But just the opposite has happened, largely because the academic medical community has itself become enmeshed in intense conflicts of interest. Without going in depth into the workings of the Bayh-Dole Act,²³ it is fair to say academic medicine today is dominated by a generation of academic entrepreneurs who have taken their government-funded intellectual property and sought to both heal the sick and make their fortunes by commercializing it. Again, I have no problem with that.

But it would be foolish to think that such endeavors do not create huge conflicts of interest: intellectual, financial and emotional. If I think C-reactive protein levels in the body are a great new way to determine if someone is going to develop a severe cardiac event, and I own the use of C-reactive protein as a biomarker for measuring that, and I have started a company with my university's help to develop and then, hopefully, sell the test to thousands of hospitals and physicians, then you can rest assured that I will be a forceful advocate—in the medical literature, in professional meetings, at federal advisory committee meetings—for that point of view, and will oppose anyone who thinks this is not something the medical system either needs or can afford.

Similarly, if I am a clinician who is actively engaged in enrolling

23. Bayh-Dole University and Small Business Patent Procedures Act, Pub. L. No. 96-517, § 6(a), 94 Stat. 3019 (1980) (codified at 35 U.S.C. §§ 200-211 (2000)).

my sick patients in industry-funded clinical trials, I not only make additional income from this activity, but I have an emotional stake in hoping that the drug being tested on my patients is going to work. Yes, the trials are double-blinded and controlled in various ways. But the possibility of bias enters the equation in numerous ways: from patient screening, to the choice of endpoints, dosing, and comparator drugs if any, to the interpretation of the resulting data. Every study that has been done on the relationship between funding sources and study outcomes has shown a positive relationship best described as “he who pays the piper calls the tune.”²⁴

Do I think the clinicians behind the VIGOR trial lied or were simply doing Merck's bidding when, in 2001, they wrote in the *New England Journal of Medicine* that the reason Vioxx had four times the cardiovascular deaths than naproxen was that naproxen was cardioprotective?²⁵ No, I think they really believed it, because their professional interests, their humanitarian interests (they believed in the underlying premise that COX-2 inhibitors would be less harsh on the stomach than ibuprofen and aspirin), and, yes, their financial interests coincided.

Four years later, when the data from this and other trials was reviewed by an outside advisory committee at the FDA, my organization revealed that ten out of thirty-two members of the committee had ties to COX-2 manufacturers.²⁶ As reported by the *New York Times*, had those votes been subtracted from the final tallies, the committee would have voted to withdraw two of the drugs, including Vioxx, from the market.²⁷ As it was, they voted for a slightly stronger warning on the label.²⁸

One recent study points out that there is no correlation between ultimate votes on FDA advisory committees and conflicts of interest.²⁹ As the argument goes: The COX-2 committee was an anomaly. The vast majority of votes are unanimous or near unanimous: Scientists with

24. See, e.g., Justin E. Bekelman et al., *Scope and Impact of Financial Conflicts of Interest in Biomedical Research: A Systematic Review*, 289 JAMA 454, 454, 456 (2003).

25. Claire Bombardier et al., *Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis*, 343 NEW ENG. J. MED. 1520, 1526-27 (2000).

26. Press Release, Ctr. for Sci. in the Pub. Interest, Conflicts of Interest on Cox-2 Panel: Research from CSPI's Integrity in Science Project (Feb. 25, 2005), <http://www.cspinet.org/new/200502251.html> (evaluating, at the bequest of the *New York Times*, scientific experts chosen by the FDA to evaluate Cox-2 inhibitors).

27. *Id.*

28. Gardiner Harris & Alex Berenson, *10 Voters on Panel Backing Pain Pills Had Industry Ties*, N.Y. TIMES, Feb. 25, 2005, at A1.

29. Peter Lurie et al., *Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings*, 295 JAMA 1921, 1921, 1925-26 (2006).

conflicts and those without vote pretty much the same—almost always for approval. But I think this kind of mechanistic analysis misses the larger point about how conflicts of interest, which are intellectual as well as financial, dominate the proceedings. These are, for the most part, committees made up of clinicians who are deeply interested in helping to develop the next new breakthrough, and are always on the lookout for better drugs. The clinicians with conflicts crowd out more critical voices who can probe the nuances in the data, who are experts in identifying safety warning signs, drug-to-drug interactions, a drug's impact on comorbidities, and other aspects of the disease that specialists may not be aware of.

IV. CONCLUSION: SUGGESTED REFORMS

My project has been heavily involved in lobbying to eliminate scientists with conflicts from FDA advisory committees for precisely this reason: It is time to open up the process to new voices with a broader range of expertise. In other words, it is time to make these advisory committees more balanced, which is also a requirement of the Federal Advisory Committee Act.³⁰

The main arguments against this reform are that all experts have conflicts of interest, and, by eliminating physicians with conflicts of interest, we will be eliminating the best and the brightest. I think this is a slander on the thousands of clinicians who conduct NIH-funded clinical trials, or who work for government organizations like the Department of Veterans Affairs ("VA") or who simply have not signed onto industry's payroll. I recently reviewed all of the conflict of interest disclosure statements for the annual American Society of Clinical Oncology meeting, which draws nearly 15,000 physicians every year to hear the latest scientific breakthroughs in cancer research. Over 700 people either led sessions or made presentations. About two-thirds of them had conflict of interest statements. This is about in line with the current mix of clinical trial funding: Industry now funds about sixty to seventy percent of clinical trials. But that means one-third of them were not conflicted. If they are qualified to make presentations to the nation's oncologists, they are equally qualified to serve on federal advisory committees evaluating new cancer drugs.

While I have spent most of my time discussing the FDA, I would be remiss if I did not point out that conflicts of interest are also major factors in the decision-making at other health related agencies like the

30. Federal Advisory Committee Act, Pub. L. No. 92-463, 86 Stat. 770 (1972) (codified as amended at 5 U.S.C. app. 2 §§ 1-15 (2000)).

Center for Medicare and Medicaid Services (“CMS”) and the Centers for Disease Control, which is a major player in vaccine development. The prohibitions in the new senior citizen prescription drug benefit,³¹ which were largely written by pharmaceutical industry lobbyists, are exhibit number one, of course. The law specifically prohibited the government from either negotiating over price or establishing a universal formulary, both of which are in common use in other advanced industrial countries and, I might add, to excellent effect at the VA.

But this is just the tip of the iceberg. Drug industry influence comes to bear on virtually all CMS coverage decisions, which are often informed by an outside advisory committee made up of physicians and economists who often have financial ties to industry. Allow me to mention just one instance where this has gone astray: Epoetin (“Epo”) reimbursement in the End Stage Renal Disease Program. Epo is a synthetic protein, usually produced in the kidneys, that stimulates the bone marrow to produce red blood cells. For years, Amgen-funded scientists conducted studies that suggested increased use of this legitimate medical breakthrough would be beneficial to these very sick patients. The trials measured subjective endpoints like alertness and energy. With results in hand (and often by bringing the clinicians who conducted the trials to Washington), they successfully lobbied the CMS to reimburse clinics for their use of Epo to the point where they raised patients’ red blood cell count to nearly normal levels. This has been very lucrative for Amgen, whose government sales of this one drug are now over \$2 billion annually. But a study that appeared in *Health Affairs* just last month showed that this policy has not been very good for patients.³² In fact, as their red blood cell counts approached normal, their mortality rates rose, which is not really that surprising given that these are people with severe microvascular distress caused by a lifetime of poorly controlled hypertension and diabetes—the two primary causes of kidney failure leading to dialysis in the government End Stage Renal Disease program.

A number of simple reforms would go a long way toward ending the conflicts of interest arising from industry’s involvement with government. First, Congress should prohibit scientists, clinicians and economists with conflicts of interest from serving on health-related federal advisory committees, especially the ones that are making science-based decisions about new drugs and devices or Medicare’s

31. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub. L. No. 108-173, § 101, 117 Stat. 2066 (codified at 42 U.S.C. § 1395w-102 (2000)).

32. Dennis Cotter et al., *Translating Epoetin Research into Practice: The Role of Government and the Use of Scientific Evidence*, 25 HEALTH AFF. 1249, 1255-56 (2006).

payment decisions.

At the same time, the government needs to generate more objective and more useful information about the drugs that are already on the market. In the process, this would provide an additional career avenue for academic physicians who want to pursue cutting-edge research. Nearly a decade ago, Princeton University health care economist Uwe Reinhardt proposed something comparable to a one percent tax on prescription drugs to fund systematic, comparative clinical trials on all the medicines that are out there so physicians will have an objective source of information when making treatment determinations.³³ This could be done at a new institute at NIH, or at academic medical centers, and rejuvenate the field of investigator-initiated clinical research.

We need to repeal PDUFA, at least as it is presently structured. If a cash-strapped Congress does not want to properly fund the FDA with unrestricted general revenue, it should at least decouple user fees from any intended use. A regulatory agency, especially one whose mission is to protect the public from unsafe or ineffective drugs, must have the freedom to make its own decisions about how to deploy its resources in carrying out that mission.

And finally, the FDA should be given the power to force industry to gather data and carry out the post-marketing clinical trials they promise at the time of approval. Indeed, the same NIH institute that carries out the clinical effectiveness trials could be given this task, thus creating another funding source for truly independent research. Ending conflicts of interest is not about some abstract notion of purity. It is about getting better science.

33. Uwe E. Reinhardt, Op-Ed, *How to Lower the Cost of Drugs*, N.Y. TIMES, Jan. 3, 2001, at A17 (suggesting that private insurers and the government devote one percent “of their collective yearly spending on prescription drugs and endow a \$1 billion research institute”).