FDA: This Agency Can Be Dangerous

Marcia Angell

Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA
by Daniel Carpenter.
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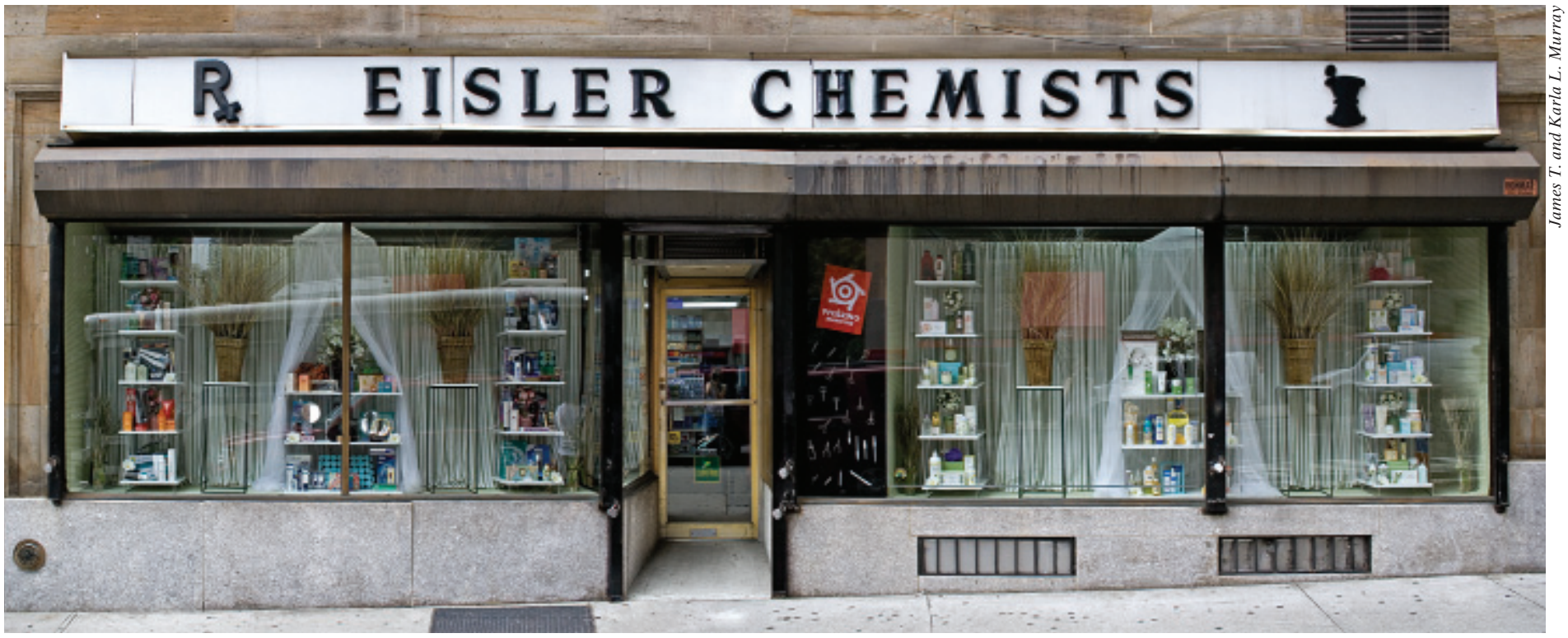
The US Food and Drug Administration (FDA) is a vital public agency. It is responsible for ensuring the safety of the foods we eat and many of the medical treatments we receive, and thereby regulates about a quarter of the nation's domestic economy. I strongly believe in the FDA's mission, and respect the many FDA employees who are dedicated to carrying it out.

But there is growing evidence that the Center for Drug Evaluation and Research (CDER, pronounced "cedar"), the part of the agency that regulates prescription drugs, has become the servant of the industry it regulates. This has resulted in the sale of drugs of uncertain benefits, some with serious side effects, and in the agency's failure to respond promptly to evidence that a drug is dangerous. There is no better example than the agency's decision to allow the diabetes drug Avandia to remain on the market after having determined three years ago that it increases the risk of heart problems and despite the existence of a similar drug that appeared safer. Even after revelations that the drug's maker, the British company GlaxoSmithKline, suppressed indications of problems and biased its research in Avandia's favor, the FDA remained reluctant to pull the drug. By the end of August it was still unclear whether the agency would remove Avandia from the market.[1]

CDER also does not fulfill its obligation to oversee the marketing of prescription drugs, thus permitting misleading drug ads and illegal practices such as drug companies inducing doctors to prescribe drugs for uses that have not been approved by the FDA. Although nearly every major drug company has paid enormous fines to settle charges of illegal marketing (Pfizer's recent $2.3 billion fine—for illegally promoting its painkiller Bextra and three other drugs—is the current record), they evidently consider the fines the cost of doing business, since the same practices keep recurring with little interference from CDER.

Americans use enormous amounts of prescription drugs. According to the Kaiser Family Foundation, 3.9 billion drug prescriptions were filled in the US in 2009, an average of 12.6 per person. Most people over age sixty-five take at least three prescription medications daily. Since the FDA is what stands between the public and an aggressive, profit-driven industry, its independence from the industry it regulates is of fundamental importance.

This is not an issue that receives much attention from Daniel Carpenter in his imposing new book, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*, nor does the related question of whether CDER is doing its job of ensuring that the drugs we take in such huge quantities are really safe and effective. Instead, Carpenter, a professor of government at Harvard, spends 752 dense, exhaustively documented pages telling the reader virtually everything else about the FDA—its history, procedures, personalities, and politics. Like much academic work on public and social policy, it strives to be impartial. But it sees complexity even when it is not there (some things about the FDA are quite simple), and it remains oddly aloof from the issues that most matter.[2] Its main value is as a reference work.



James T. and Karla L. Murray

Lexington Avenue at East 79th Street, New York City, 2008; photograph by James T. and Karla L. Murray from their book Store Front: The Disappearing Face of New York, *published last year by Gingko Press*

Here I'll discuss the problem that Carpenter largely neglects—how to ensure that CDER, free of industry influence, protects the public from unsafe and useless drugs.

CDER consists of several sections, the largest of which is the Office of New Drugs (OND), which has responsibility for approving new drugs and deciding what action to take when a drug already on the market is found unsafe. Other sections monitor drugs for safety, approve generic drugs, oversee marketing, and ensure quality in manufacturing plants.

By law, before a drug company can sell a drug, it must sponsor clinical trials to prove to CDER that the drug is reasonably safe and effective. CDER usually requires only that the trials compare the new drug with a placebo, not with existing drugs. (This minimal standard means that most new drugs merely have to be better than nothing, which makes it possible for companies to turn out trivial variations of top-selling drugs, called "me-too" drugs, instead of innovative ones.) Before these "pre-marketing" trials begin, a drug company must file an "investigational new drug" application (IND), which describes the proposed research, including measures to protect the welfare of human subjects.

After the trials are completed, which usually takes a few years, the company must file another application, called a new drug application (NDA), to get approval to go to market. With the help of advisory committees of outside experts, CDER staff reviews the NDA, including the results of the clinical trials. The review process is relatively fast, usually taking about a year and sometimes as little as a few months.

Only if the drug passes this scrutiny is it allowed to be sold, and it is then given exclusive marketing rights for a specified time, usually five years (twelve years for biotech drugs, which are large molecules, usually made from living biological systems). Sometimes, drug companies may be asked to conduct "post-marketing" studies to make sure a drug is safe after it comes into widespread use. Generic drugs are copies of brand-name drugs whose exclusive rights have expired. They, too, need CDER approval, which requires their manufacturers to show that they are essentially the same as the brand-name drugs they copy. Companies are permitted to promote drugs only for the uses for which they were approved, although once on the market, doctors may prescribe them for any reason they choose.

Industry influence on the FDA is exerted in two major ways—first, through congressional legislation largely dictated by industry lobbyists, and second, through administrations that are beholden to industry, and sometimes, as in the case of the George W. Bush

[1]For an overview of the Avandia story, see Clifford J. Rosen, "Revisiting the Rosiglitazone Story—Lessons Learned," *The New England Journal of Medicine*, August 26, 2010. Rosen was chairman of the FDA advisory committee that concluded in 2007 that Avandia increased the risk of heart problems. See also Gardiner Harris, "Diabetes Drug Maker Hid Test Data, Files Indicate," *The New York Times*, July 12, 2010; and the Senate Finance Committee's "Staff Report on GlaxoSmithKline and the Diabetes Drug Avandia," January 2010.

[2]An earlier book, Philip J. Hilts's *Protecting America's Health: The FDA, Business, and One Hundred Years of Regulation* (Knopf, 2003; University of North Carolina Press, 2004), managed to be both less comprehensive and more informative about the central issues.

administration, openly hostile to the very idea of regulation. The result is a climate in which CDER employees are inhibited from acting against drug company interests even when the agency has legal authority to do so. In addition, drug companies spend millions of dollars to directly lobby the FDA, even though it seems improper to permit a lobbyist to walk in the door of a regulatory agency.

The Obama administration is friendlier to regulation than was the Bush administration. The new FDA leadership has taken steps to make the agency's actions more transparent, and has set up a program for doctors to report misleading drug ads. But to my knowledge, there has been little substantive change in CDER's organization or procedures, and it retains the same director.

The following are nine reforms that I believe would greatly strengthen CDER, protect it from industry influence, and enable it to do its job better. Although Carpenter describes many of the conditions that make reform necessary, he does not adequately examine the underlying issues, nor does he recommend solutions. Some of the reforms I suggest would require congressional legislation, some would not, and others might.

First, the Prescription Drug User Fee Act (PDUFA) should be repealed. This legislation, which Congress enacted in 1992 and must be renewed every five years, authorizes drug companies to pay CDER for reviewing their drugs. But the payments are made under terms largely set by the industry. PDUFA greatly extended the industry's influence. Even the name of the act suggests that CDER's "users" are drug companies, not the public, and sadly that seems to be the case. The drug companies pay fees for each drug reviewed, so it is in the agency's interest to review as many drugs as possible as quickly as possible. Approval is faster than disapproval, since it produces no argument from the company. Originally, the act stipulated that the money could be used only to speed review of drugs to meet industry-approved goals. Since 2002, a small fraction may be used for safety monitoring, but most is still directed toward drug approval. Fees paid by private companies now account for more than half of CDER's budget.

Immediately after PDUFA was enacted, CDER began to hire large numbers of new drug reviewers. As staffing for drug approval grew, staffing languished for equally important functions—such as ensuring drug safety, approving generic drugs, reviewing advertising for accuracy and balance, and inspecting manufacturing plants. As of the first of the year, the Office of New Drugs, which approves brand-name drugs, had 930 employees, while the Office of Surveillance and Epidemiology (OSE), which monitors the safety of drugs on the market, had only 206. The Office of Generic Drugs (OGD) had 268, the Division of Drug Marketing, Advertising, and Communication had fifty-one, and the Division of Manufacturing and Product Quality (DMPQ) had eighty-three.[3]

[3]These figures were provided to me by CDER in January 2010. For additional footnotes see the Web version of this review at www.nybooks.com.

This staffing is manifestly unbalanced. How, for example, can only fifty-one people ensure that tens of thousands of ads and promotional campaigns accurately convey the balance between risks and benefits of prescription drugs? Similarly, how can a staff of only eighty-three possibly ensure that the thousands of foreign manufacturing plants under its purview follow good manufacturing practices?

The FDA should be much better funded by Congress, and the balance of functions within CDER should be restored, so that the Office of New Drugs is no longer the tail wagging the dog. Four former FDA commissioners have agreed that the agency should be entirely publicly funded, and they are right. Under PDUFA, private companies pay CDER about $400 million a year, but I strongly doubt that taxpayers come out ahead. If we want better, safer, and cheaper drugs, Congress should appropriate that additional amount, and more. Carpenter discusses PDUFA, but with little apparent concern for its pernicious effect on the agency's independence and effectiveness.

Second, the Office of Surveillance and Epidemiology (OSE) should have more authority and independence from the Office of New Drugs (OND). This office, which is concerned with drug safety, has no direct regulatory authority, but serves only to advise the OND. Decisions to withdraw drugs or restrict their marketing or labeling are the responsibility of the OND. That is plainly a conflict of interest, since the same office that approves drugs is then responsible for revising and possibly overturning its own decisions.

Carpenter describes this problem at length, but makes no recommendation for solving it. Some critics have advocated a new agency to oversee post-marketing drug safety. I don't think that is necessary, but I do believe the OSE should be given final authority for monitoring and regulating the safety of drugs after they come on the market, with the OND serving in an advisory capacity. The post-marketing relationship between the OND and the OSE would then be the reverse of their relationship before drugs reach the market.

Third, members of CDER's standing advisory committees should have no financial ties to drug companies (except for research support provided under carefully restricted conditions). According to the reporter Merrill Goozner, in 2006 some 30 percent of all advisers disclosed conflicts of interest, and in 75 percent of committee meetings at least one voting member did so. Although advisers are not supposed to vote on matters involving companies with which they are financially associated, waivers are granted so frequently as to be almost routine.

Conflicts of interest matter. Consider the case of Vioxx, the arthritis drug that was removed from the market in 2004 because it was associated with an increased risk of heart attacks and strokes. In 2005, a special FDA panel, consisting of two of the standing advisory committees, held public hearings to consider whether Vioxx and two other drugs in the same class, Bextra and Celebrex, were safe enough to stay on the market. After three days, the panel recommended that all three drugs be allowed on the market, perhaps with strong warnings on the labels and a moratorium on advertising directly to consumers.

About a week later, however, *The New York Times* revealed that ten of the thirty-two members of the panel had financial ties to the makers of the drugs. If their votes had been discounted, the panel would have recommended that only Celebrex stay on the market. In a departure from its usual practice, CDER, no doubt embarrassed, rejected the advice of the full panel and allowed only Celebrex to stay on the market. If not for the revelations in *The New York Times*, the decision would probably have gone the other way.

The story of how Vioxx came to market in the first place is even more damning. It was approved in 1999, after the approval of Celebrex. Even though it was the second drug in the class, neither of which had been shown to be better or safer than over-the-counter drugs for pain relief, Vioxx was given a rapid review (called a "priority review") by CDER. The FDA's minutes of the advisory committee meeting that led to its approval revealed that four of the six members, including the chairman, were given waivers, because they had "a potential for a conflict of interest." Although Carpenter discusses Vioxx in some detail, he inexplicably omits mention of these conflicts of interest.

The new FDA guidelines concerning conflicts of interest, issued in 2007, are hardly reassuring. They allow up to a $50,000 interest in relevant companies—for example in consulting fees or stock ownership—and call for limitations on the number of waivers granted. That's a very weak reform. Some of our best medical schools now have much tighter restrictions on investigators' financial ties to the sponsors of their research beyond support for the research itself. The position of FDA advisers should be analogous. In both cases, a drug is being evaluated by experts who should have no financial interest in the outcome of their recommendations.

Members of advisory committees should be permitted to accept research grant support from industry. But when they do, they should be barred from any FDA meetings involving that company, and of course, they should have no other financial associations with industry. There should be no waivers; no one is indispensable. Apologists often claim that it is impossible to find experts who don't have financial conflicts of interest. When I was editor of *The New England Journal of Medicine*, I often had to find such experts to write editorials for the journal, because our policy prohibited authors of editorials from having conflicts of interest. Finding them was sometimes difficult, but not impossible. If the FDA insisted that its advisers not have conflicts of interest, it would probably have a salutary effect on the larger medical community, since serving on FDA advisory committees is considered to be prestigious.

Fourth, the FDA should see that the post-marketing studies it requires as a condition of approval are carried out in a reasonable time. Some drugs are now approved on the basis of only one or two short clinical trials, or trials that use "surrogate endpoints." (A surrogate endpoint is an outcome, like cholesterol level, that is probably correlated

with a clinical outcome, like heart attack, but isn't itself a clinical outcome.) When drugs receive such fast-track approval, sponsors agree to conduct post-marketing studies to ensure that the drugs are safe and effective after they are in widespread use. However, drug companies regularly disregard this commitment. As of 2008, there was reportedly a backlog of more than 1,200 required post-marketing studies, of which 900 hadn't even been started.

CDER often asserts that it does not have the legal authority to enforce the completion of these studies. But it does have the authority to withdraw drugs from the market, and that threat ought to persuade drug companies to honor their commitments. Carpenter devotes a long chapter to post-marketing regulation, and seems to agree that the FDA could force the completion of these studies but is constrained from doing so by fear of the political reaction. He's probably right about that.

CDER has never pulled a drug off the market because of a company's recalcitrance in conducting a post-marketing study. It should. If drug companies know the FDA will never use its authority in this way, they have no incentive to meet their commitments. In the case of me-too drugs, which by definition do not fill unmet needs, failure to meet a commitment to do a post-marketing study should result in withdrawal of the drug from the market. In the case of innovative drugs, of which there are relatively few, there should be heavy and escalating fines for noncompliance.

Fifth, approval of new drugs should be limited to three years, and during that time advertising aimed directly at consumers should be prohibited. A similar reform was recommended in the Institute of Medicine's 2006 report "The Future of Drug Safety: Promoting and Protecting the Health of the Public." During those three years, the OSE would collect information on safety, using databases such as those maintained by large health facilities like Kaiser Permanente. Continued approval after three years would be contingent on a favorable balance between risks and benefits. During this probationary period, direct-to-consumer ads should be banned. Too often, these ads aim to convince people that they have medical conditions requiring drug treatment they would not otherwise seek, thus unnecessarily risking side effects not yet identified. Carpenter does not discuss the issues raised by ads aimed directly at consumers.

Sixth, the FDA should review generic drugs as rapidly as brand-name drugs, and be adequately staffed to do so. It currently takes more than twice as long to review generic drugs as brand-name drugs, and there is a backlog of some 1,900 of them waiting to be reviewed. This disparity between the leisurely pace of getting generic drugs on the market and the rush to approve brand-name drugs is indefensible. It merely protects brand-name profits. The excuse that it is more important to get brand-name drugs on the market because they offer innovative treatments is not persuasive. About 80 percent of newly approved brand-name drugs are classified by CDER as appearing "to have therapeutic qualities similar to those of one or more already marketed drugs"—that is, they do not fill unmet needs and most often are me-too drugs. Given the staggering costs of brand-name drugs to consumers, it's at least as urgent to get generic drugs on the market. Carpenter does not discuss the FDA's responsibility for the approval of generic drugs, much less discuss the disparity in approval times.

Seventh, in pre-marketing trials, me-too drugs should be compared with an existing drug to treat the same condition, not just with a placebo. Me-too drugs are now the major output of the pharmaceutical industry. It is too late to wait until they are on the market to compare them with existing drugs. Once drugs are aggressively promoted, it is very difficult to counter sales pitches with data from comparative studies. Sometimes, a pre-marketing trial should compare a new drug with both a placebo and an existing drug, because there may be doubts about the effectiveness of the older drug or the whole class of drugs. The agency should have considerable discretion in deciding whether to approve another me-too drug. If, for example, it is no more effective than its predecessors, but substantially more convenient or has fewer side effects, then it should be approved. But if it is no better in any way, and there are already several similar drugs on the market, it should be rejected.

If me-too drugs were limited, there would be more pressure to develop innovative drugs, fewer clinical trials of no medical importance, and far fewer expensive and misleading promotional campaigns. Over the past three decades, the industry has shifted its focus from trying to discover innovative drugs to producing me-too drugs, many for vague or minor conditions. Companies use their marketing muscle to expand sales, and often sales grow not just for the advertised drug, but for the others in the same class made by other companies. Carpenter does not see this as a problem, but he is wrong. Not only are people taking more and more drugs of marginal benefit, but we are seeing less and less innovation from the industry.

The eighth reform concerns the "surrogate endpoints" I mentioned earlier. As I noted, these are measurements that are thought to predict clinical results in drug tests. For example, in a trial of a drug to prevent heart attacks, the outcome measured might be cholesterol levels instead of actual heart attacks. Or in a trial of a cancer drug, the outcome measured might be the size of a tumor, not length of survival. But surrogate endpoints do not always have the expected predictive value. It makes sense to rely on them in clinical trials of drugs to treat serious conditions for which there are no existing treatments, because such trials are faster, even if sometimes misleading. (Even then, post-marketing studies should always be required to check clinical outcomes.) But for me-too drugs or drugs for less serious conditions, there is no rush and the FDA should insist on clinical endpoints. Although Carpenter discusses surrogate endpoints at length, he does not say whether their use should be curtailed.

Ninth, as a condition for enrolling human subjects, all clinical trials, without exception, should be registered at inception in a public database and the results shown when the research is completed. If drug companies or their agents ask members of the public to participate in research, they have an obligation to make the design and outcome of the work publicly accessible, along with disclosure of investigators' conflicts of interest. The industry contends that registering all clinical trials would harm companies' proprietary interests. But by the time clinical trials begin, drugs are already patented; further secrecy is unjustified and may run counter to the public interest. Suppose, for example, a competitor learns something from a company's experience that would enable it to avoid pitfalls in its own research. While that might be detrimental to the first company's competitive position, it might also speed the process of getting a good drug to market. The FDA should not put proprietary claims ahead of the public welfare, as I believe it sometimes does. Carpenter does not address the issue of registration of clinical trials.

There is a widespread belief within CDER that the pharmaceutical industry and the FDA are engaged in a common endeavor—that they're "partners." I've even heard a senior FDA official refer to drug companies as the agency's "clients," and another assert that the agency's job is to "facilitate drug development," which is different from regulating it. This confusion is probably greatest at the upper levels of the agency, which are most vulnerable to industry pressures. In 2003, the Health and Human Services inspector general found that 18 percent of CDER reviewers felt pressured by their superiors to recommend approval of drugs against their better judgment.

The pharmaceutical industry and the FDA are *not* engaged in a common endeavor, and they shouldn't be. Drug companies, of course, want to sell safe and effective drugs, but their primary purpose, like that of other investor-owned businesses, is to enhance the value of their shareholders' stock by maximizing profits. If they did not do that, their top executives would risk being fired. The job of regulators, on the other hand, is to enforce legal constraints that often moderate the profit incentive. Thus, the basic missions of industry and regulators are different, and inherently somewhat adversarial, no matter how pleasant the relationship. No business likes having its profit-seeking activities curbed by external rules, and industries almost always resist government regulation. But self-regulation is an illusion, as we learned from the collapse of the financial industry and the oil spill in the Gulf of Mexico. There must be some tension between the pharmaceutical industry and the FDA. If there is not, the FDA is not doing its job.

A book on the FDA's regulation of prescription drugs cannot be complete without confronting the extent to which the agency's responsibilities have been distorted by the pharmaceutical industry. Carpenter provides a vast store of information about the FDA, its history, and its politics, but he avoids taking positions on important issues or suggesting remedies. Instead, he seems determined to maintain a detached neutrality. That is a great pity, because the FDA's failures are of immense public importance and deserve full exploration in a work as ambitious as this one. □

—September 1, 2010