

INVESTIGATOR AWARDS IN Health Policy Research

The U.S. Food and Drug Administration (FDA) is one of the world's most powerful regulatory agencies. No new drug can be marketed legally in the United States unless the FDA declares it to be "safe and effective" for its intended uses. Having set the scientific standards and processes for drug approval, the FDA has played a key role in the industry's evolution worldwide and shapes how pharmaceutical companies develop, market, and manufacture their products. More subtly, the FDA undergirds public confidence in pharmaceuticals.

According to Daniel Carpenter, the Allie S. Freed Professor of Government and Director of the Center of American Political Studies at Harvard University, the primary source of the agency's power is its professional and scientific reputation, carefully cultivated over time and guarded by FDA career officials.

But how did the FDA's reputation invest it with so much influence? And how exactly does the FDA wield its extraordinary power? Carpenter has probed these and other intriguing questions about the FDA's history, evolution and behavior, more deeply perhaps than any other scholar ever.

Carpenter traces the roots of his interest in the curious and sometimes troubled intermingling of regulation, power, and politics to his grandfather, Edward Krumbiegel, who served for 33 years as health commissioner for the city of Milwaukee, Wisconsin. The stories he heard from his grandfather and from his mother, Kathleen, who worked as a radiologist, about battles over fluoridation, pest control, and other public health issues led him to understand early on that health policy does not emerge purely or even largely from the world of science. "I learned that public health was an endeavor not only of science, but of politics in its best and worst aspects," Carpenter says.

Reputation and Power

Now a leading authority on pharmaceutical regulation in the United States, Carpenter has published a book with the support of a Robert Wood Johnson Foundation Investigator Award in Health Policy Research that serves as a comprehensive treatise on the FDA. *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA* chronicles the FDA's rise to extraordinary influence, the enormous impacts it has had on the pharmaceutical world, the challenges the agency has weathered over the past few decades, and its weakened status today.

Carpenter links the first major expansion of the FDA's regulatory powers and enhanced reputation to a highly publicized tragedy in 1937 involving the deaths of hundreds of people who took a toxic "elixir" containing improperly prepared sulfanilamide. The FDA's central role in the sulfanilamide episode — from recalling the product to serving as a trusted information source for the public during the crisis — helped shape opinion about the need for greater protection against dangerous drugs. In response, Congress in 1938 passed the Food, Drug, and Cosmetics Act, which required companies to obtain FDA approval before bringing any new drug to market.

With sole authority to approve or reject any new pharmaceutical product, the FDA was empowered to be the "cop, gatekeeper, and protector" in the pharmaceutical world, Carpenter says. By the 1950s, the FDA was able to leverage its well-established reputation to extend its regulatory reach. By requiring increasingly high scientific standards for determining not only safety but efficacy — evidence that a proposed drug worked for its intended use — the FDA dramatically changed the rules for drug approval.

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National Program Office:
Rutgers, The State University
of New Jersey

Institute for Health, Health Care Policy,
and Aging Research

55 Commercial Avenue, Third Floor
New Brunswick, NJ 08901

phone: 732.932.3817

fax: 732.932.3819

email: depdir@ifh.rutgers.edu

www.investigatorawards.org

For example, “expert opinion” no longer sufficed for manufacturers to win approval of their products. Instead, the FDA insisted on a sequence of rigorous, controlled trials – in other words, cold, hard scientific evidence where each test built upon previous tests. Chagrined manufacturers responded by re-organizing themselves to conduct the types of research and trials required for FDA approval and hiring the types of scientists valued so highly by the FDA.

The thalidomide tragedy of the early 1960s elevated the agency’s reputation even further. More than 20 countries had approved thalidomide, the so-called “morning sickness” drug, which later was linked to thousands of horrifying birth defects. But the FDA had refused to approve the drug, insisting on more safety studies, thus sparing the American public the pain and suffering visited upon so many other countries. Carpenter writes that media coverage of the thalidomide story “reinterpreted ‘bureaucratic nitpicking’ and deliberation ... as modern-day, scientific virtues that upheld protection of American families and infants.”

But reputation can be ephemeral. The FDA’s efforts to protect the American public from unsafe drugs have constantly faced challenges – including not only the predictable assaults from the pharmaceutical industry, but also less obvious ones from advocates demanding speedier reviews for potentially lifesaving drugs. For the FDA, the struggle to strike the right balance between making effective cures available to the public as soon as possible without endangering public safety has been a costly one.

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The Erosion of Reputation and Power

Evidence of the power of the FDA’s reputation can be found, ironically, in the damage it has sustained in recent years. Carpenter traces the beginning of that decline to the 1980s, when cancer and AIDS activists assailed not the agency’s scientific reputation, but its moral reputation, arguing that the lengthy review process harmed the public by delaying access to medicines perceived as a “last hope” for the terminally ill. “There is no question on the part of anyone fighting AIDS that the FDA constitutes the single most incomprehensible bottleneck in American bureaucratic history – one that is actually prolonging this roll-call of death,” said AIDS activist Larry Kramer in a 1987 *New York Times* article.

Carpenter writes that “[t]he intertwined sagas of cancer and AIDS transformed the sufferers of diseases into political communities.” Their attacks on the agency’s moral reputation were much more powerful than previous attacks by the pharmaceutical industry criticizing long drug reviews.

Partly as a result of activists’ criticisms, Congress enacted in 1992 the Prescription Drug User Fee Act (PDUFA), which for the first time subjected the FDA to deadlines for completing drug reviews. In essence, the law brokered a deal with the pharmaceutical industry to pay user fees in exchange for speedier drug reviews – a severe blow to the agency’s power.

No longer could the FDA claim independence from the drug industry. Writes Carpenter: “In image, what was meant to be a tax on drug companies ended up being a mode by which these companies’ resources constituted the FDA budget ... The user fee law tied the agency to [manufacturers] by tying a critical source of resources to them.”

The PDUFA set up another, equally intractable conflict for the agency. The revised review process that resulted in part from the criticisms of AIDS activists may have produced rushed decisions that have endangered consumers – and, coincidentally, further damaged the FDA’s reputation. As Carpenter’s research has shown, the discovery of safety problems is more likely for drugs approved immediately before a deadline.

Once weakened, the FDA's reputation was vulnerable to other types of attacks as well, particularly in light of controversies such as that surrounding the painkiller Vioxx, which shone a critical spotlight on the FDA's scientific credibility and its impartiality. Vioxx was manufactured and voluntarily withdrawn in 2004 by Merck after concerns surfaced regarding increased risk of heart attack and stroke linked with long-term, high-dosage use. Tens of thousands of people are believed to have died from strokes or heart attacks as a result of taking Vioxx. It turned out that not only was Merck aware of Vioxx's dangers before the drug went to market – from the company's own studies – but so was the FDA.

Vioxx had nearly the same level of impact on the FDA's reputation as thalidomide – but completely opposite. Media and Congressional inquiries focused on the fact that high-ranking FDA officials overruled the recommendations of agency experts for a “black box warning” or for removing high-dose formulations from the market. The debate quickly broadened to questions about the agency's willingness to review its pre-market approvals when presented with evidence of serious safety problems.

More trouble ensued when then-FDA Commissioner Lester Crawford overruled agency experts in rejecting over-the-counter sales of the so-called “morning after” birth control pill levonorgestrel, also known as “Plan B.” Crawford's decision sparked a spate of criticism in the media and medical journals that politics had trumped science. Shortly afterward, Crawford himself resigned amid questions that he had failed to fully disclose his ties with industry.

The Vioxx scare, combined with perceived politicization of the agency's scientific decisions, caused an outpouring of concern that a 2006 Institute of Medicine report described as a “perception of crisis that has compromised the credibility of the FDA.” Carpenter documents how, in the fallout from these controversies, numerous stakeholders – including the pharmaceutical industry – worried that FDA approval would lose its “gold standard” status for drug safety and efficacy. Supreme Court Justice John Paul Stevens expressed less restraint in a footnote to the majority opinion in *Wyeth vs. Levine*, where he drew attention to “serious scientific deficiencies” at the FDA and a lack of “clear and effective process for making decisions about, and providing management oversight of, post-market safety issues.”

Today, Carpenter writes, the FDA's reputation “has been badly withered” at virtually every level: moral, scientific, and professional. But there is cause for hope. The agency is under new leadership, as part of an administration that favors greater government regulation. One of the agency's longest-running and most public battles – its campaign to secure regulatory authority over tobacco products – ended with an FDA victory in 2007, when a Democratic-controlled Congress finally passed the Family Smoking Prevention and Tobacco Control Act. In addition, an initiative to increase transparency at the FDA may help restore its tarnished reputation.

Carpenter, for one, would like to see a stronger FDA. He believes that the public's interest is served by the FDA's uniquely authoritative voice in the world of medicine. “At its best,” he writes, “the power of the Food and Drug Administration ... reflects not only the advancement of modern science, but the traditions and theories of republican government. For pharmaceuticals as for other forms of activity governed by the state, the central criterion of sound governance is not mass or breadth, but legitimated vigor.”

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About the Investigator

Daniel P. Carpenter is the Allie S. Freed Professor of Government and Director of the Center for American Political Studies in the Faculty of Arts and Sciences at Harvard University. He graduated from Georgetown University and received his doctorate in political science from the University of Chicago. He taught previously at Princeton University and the University of Michigan, joining Harvard in 2002. His dissertation received the 1998 Harold D. Lasswell Award from the American Political Science Association and as a book—*The Forging of Bureaucratic Autonomy: Reputations, Networks and Policy Innovation in Executive Agencies, 1862-1928*—was awarded the APSA's Gladys Kammerer Prize as well as the Charles Levine Prize of the International Political Science Association.



Dr. Carpenter has played an influential role in recent policy debates surrounding pharmaceutical regulation. His expert advice has been sought by congressional committees, the Institute of Medicine, the General Accounting Office, the Council of Economic Advisors, and even the Food and Drug Administration (FDA). His new book, *Reputation and Power: Organizational Image and Pharmaceutical Regulation at the FDA*, has been hailed by several reviewers as the most comprehensive and detailed study of the FDA to date and one of the best analyses of any American regulatory agency.

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