

## Virtual Mentor

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### Policy Forum

#### Reputation, gatekeeping and the politics of post-marketing drug regulation

by Daniel Carpenter, PhD

The withdrawal of Merck's Vioxx (rofecoxib) in September 2004 has occasioned a series of discussions about the institutions of pharmaceutical regulation in the United States and around the globe. The U.S. Senate Finance Committee, under the chairmanship of Charles Grassley (R-Iowa), has held several high-profile hearings on the issue. This past April, the General Accounting Office (GAO) issued a report that was highly critical of existing policy and suggested several reforms, including expanded FDA authority to require that post-market studies be carried out by drug companies [1, 2]. These ongoing policy initiatives have been accompanied by proposals from prominent medical academics and medical journal editors for the creation of a drug safety office or commission that is independent of the FDA, or at least of its drug approval divisions [3-6].

The current dilemma—and its embedment in the conflict between pre-market approval and post-market surveillance—has a long history. For several decades now, critics and observers of U.S. pharmaceutical regulation have singled out the post-marketing surveillance system for complaints. And their conclusions, while varied in some respects, have often revisited the perceived conflict between pre-market and post-market processes. Consider for example the late 1970s and early 1980s. In September 1979, the Drug Regulation Reform Act of 1979—which would have equipped the FDA with authority to require post-marketing surveillance studies for up to five years after approval and would also have loosened the standards for post-market withdrawal—passed the Senate (it would never pass the House and hence never became law). One year later, the Joint Commission on Prescription Drug Use proposed a “national Center for Drug Surveillance (CDS)” —an agency independent of the FDA’s new drug review divisions—that would “perform and encourage research into drug effects” [7-9].

The promise and the perils of efforts to reform post-marketing regulation are linked to two related and deeply patterned features of U.S. pharmaceutical regulation. The first is organizational reputation—one of the most powerful forces animating and constraining government agencies, indeed, any complex organization. The second force is gatekeeping—the fact that the FDA’s primary power over prescription drugs is exercised before the drugs reach the market.

1. *Organizational reputation and post-market surveillance.* The FDA's public reputation as patient and consumer protector in the American health care system is a powerful one, and the incentives for its protection consciously and unconsciously influence much regulatory behavior. Indeed, while the usual conflict of interest debates in drug regulation pertain to advisory committee representatives who have received industry money, the vesting of authority over post-marketing surveillance in the Office of New Drugs creates a different but no less powerful conflict of interest that current policy does not recognize. The very office of the FDA that approves new drugs—and which therefore has the least reputational incentives to revisit its past approval decisions—is also the office with legal authority over post-marketing [10]. As the GAO has recognized, the FDA's Office of Drug Safety, which houses the agency's epidemiologists and its major capacities for post-market surveillance, is only a weak consultant to the Office of New Drugs.

It is perhaps audacious to claim, and certainly difficult to prove, that reputational incentives weaken the Office of New Drugs' willingness to scrutinize drugs that have already been approved. Yet characterizations to this effect have been with us for 50 years—from medical reviewer John Nestor's 1963 testimony before Congress that FDA medical reviewers were discouraged from revisiting past approval decisions, to David Graham's lament that “the new drug reviewing division that approved the drug in the first place and that regards it as its own child, typically proves to be the single greatest obstacle to effectively dealing with serious drug safety issues” [11]. FDA observers and FDA officials themselves have consistently pointed to institutional reluctance to revisit past decisions [11, 12]. One need not agree entirely with either Nestor's or Graham's broader arguments to see the plausibility of their depictions of the FDA.

2. *Gatekeeping and the asymmetry of power.* The New Drug Application (NDA) is the central document, and in some ways the central procedural institution, of U.S. pharmaceutical regulation. It is the authority of the FDA to render a company's NDA effective that gives the agency gatekeeping power over the U.S. health care system. Once a drug is approved, much of the FDA's power over pharmaceutical companies is lost, and so are the incentives of pharmaceutical companies to behave in strict conformity with FDA wishes. When the FDA wishes a company to tweak a Phase II or Phase III clinical trial, or to gather additional information on a drug *before* an NDA is approved, pharmaceutical sponsors respond quickly and completely. Once the drug is “past the gate,” however, this behavior changes. The best example of this lies in the low initiation and completion rate of Phase IV studies. Of the 1,191 Phase IV post-marketing commitments that had been made as of Sept. 30, 2004, 68 percent had not been started. [13, 14].

As is it is currently endowed, the FDA can do little about such patterns. The set of punishments available to the FDA is brute, not nuanced. Faced with a noncompliant firm that refuses to honor its Phase IV commitments, the FDA cannot issue fines, restrict advertising or impose any administrative penalty save that of suspending the company's NDA. The political incentives weighing against NDA suspension—as

well as the punishment this delivers to patients and their physicians—render Phase IV commitments essentially unenforceable.

I have no confident predictions to offer regarding the future of policy reforms. As long as reputational incentives govern the FDA, there will be conflict between those who approve drugs and those who scrutinize those same drugs once they have entered the market. And as long as the FDA's authority remains weighted toward pre-market approval, the agency will have a difficult time inducing optimal behavior by firms. The United States will likely remain mired in its current dilemmas, without effective policy options to combat post-market safety troubles.

### Notes and References

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7. For a concise and summary historical review of 1970s efforts to reform post-marketing regulation, see U.S. Congress, Office of Technology Assessment. *Postmarketing Surveillance of Prescription Drugs*. Washington, DC: US Government Publishing Office; 1982.
8. After hearings before the Subcommittee on Health of the Senate Committee on Labor and Human Resources in 1974, the Department of Health Education and Welfare created a review panel on new drug regulation, which issued its report in May of 1977. Lawmaking in the Senate followed this report in the subsequent session of Congress.
9. See Appendix B of the OTA Report, *Postmarketing Surveillance of Prescription Drugs*, Conclusions and Recommendations of the Joint Commission on Prescription Drug Use. Jan. 23, 1980. U.S. Congress, Office of Technology Assessment. Washington, DC: US Government Publishing Office; 1982.
10. US General Accounting Office. *Drug Safety*. 2006:19.
11. For Graham's remark, see United States Senate Committee on Finance Web page. *Testimony of David J. Graham, MD, MPH, November 18, 2004*. Available at: <http://finance.senate.gov/hearings/testimony/2004test/111804dgtest.pdf>. Accessed May 1, 2006.
12. See Nestor's remark in 1963 that “although my frankness was acceptable before I

was hired, after joining the organization I found that any medical opinion that raised issues that involved reappraisal of past decisions, past policies, or past commitments to the pharmaceutical industry would be challenged—not in a healthy scientific atmosphere, but, rather, with indifference, disapproval, or even hostility.” Later in the same hearing, Nestor remarks that “What the problem seemed to be was that in making present decisions, it was sort of sacrosanct situation that we were not to question decisions made in the past.” See Interagency Coordination in Drug Research and Regulation. *Hearings Before the Subcommittee on Reorganization and International Organizations of the Committee on Government Operations. Part 3, The Bureau of Medicine in the Food and Drug Administration.* US Senate, 89th Congress, 1st Sess, (March 20, 1963):783, 790.

13. For data on Phase IV completion, see *Federal Register* 70 (33) February 18, 2005: 8030.

14. See *Comments of Consumers Union before the Food and Drug Administration Science Board.* April 15, 2005: 8-9. Available at: [http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4136OPH\\_02\\_01\\_Consumer's%20Union.pdf](http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4136OPH_02_01_Consumer's%20Union.pdf). Accessed September 8, 2005.

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