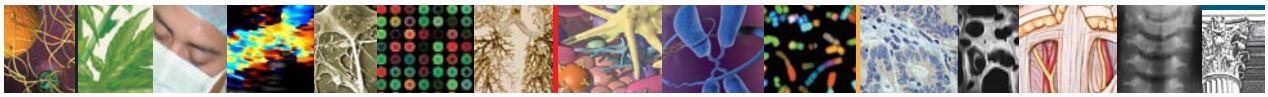

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Perspective

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Paying for Drug Approvals — Who's Using Whom?

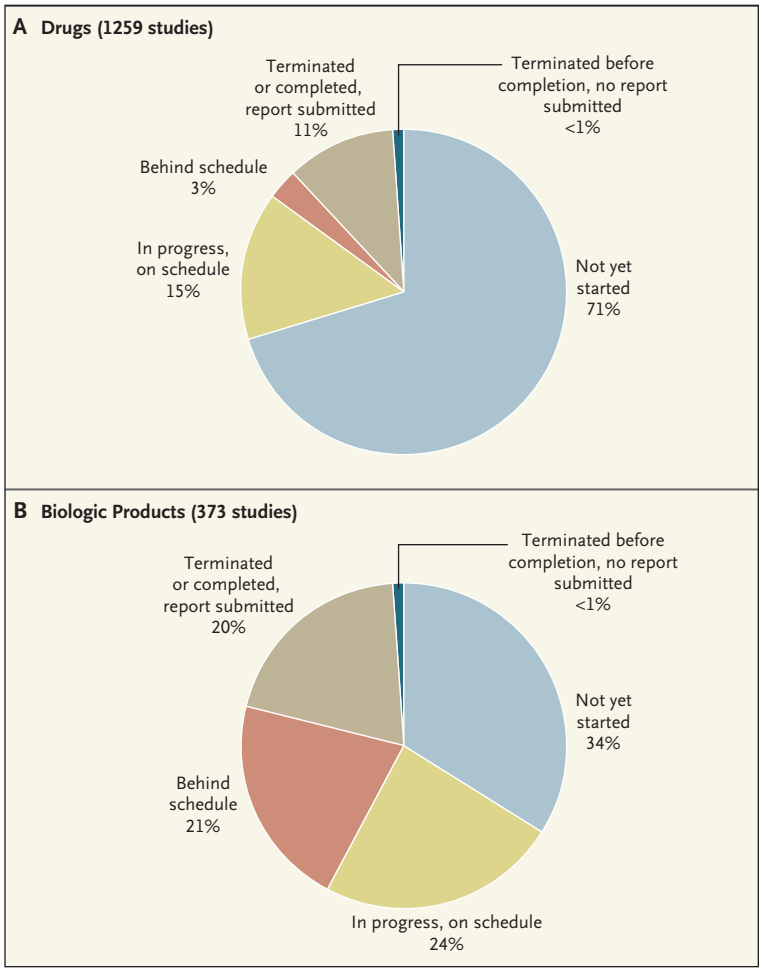
Jerry Avorn, M.D.

Years ago, an administrator at a community hospital explained to me how well his institution's grand-rounds program worked. "The drug companies find the speakers, pay their honoraria, and provide free food for the doctors, which helps a lot with attendance," he said. "It works well for us, especially with our budgets so tight." Yet those lunches were actually quite costly for the hospital: attendees at such events predictably go on to prescribe the products promoted there — which is precisely why the drug companies so willingly pay for these programs.

This penetration of commerce into the province of science isn't limited to continuing medical education. Since 1992, the United States has relied heavily on the pharmaceutical industry to pay the salaries of Food and Drug Administration (FDA) scientists who review new drug applications. The Prescription Drug User Fee Act (PDUFA) is now up for its periodic 5-year renewal, and Congress seems ready to reauthorize it with the same short-sightedness that afflicted that naive hospital administrator.

PDUFA was enacted at the end of the presidency of George H.W. Bush, when many in Washington believed that government was at the root of most of the country's problems. At that time, the FDA was having difficulty evaluating new drugs quickly and efficiently. The agency had been shaken by sit-ins held by AIDS activists protesting long review times, which they argued were killing them. The staff of the FDA was too small to adequately assess all the new drug applications the agency received. But the era's dominant ideology derided "bloated government" and demanded that Congress rein in "runaway spending." In that climate, the sensible policy solution — provide the FDA with more federal funding to hire enough people to carry out its mission — was a nonstarter. But just as the FDA's slowness may have been costing patients with AIDS their lives, it was costing pharmaceutical manufacturers their income. So the industry stepped in and helped to design a plan under which companies would pay the salaries of agency employees who reviewed the companies' submissions.

There were problems with the user-fee approach from the beginning. The original legislation required that no portion of com-



Status of Open Commitments for Postmarketing Studies Requested by the FDA, as of September 30, 2006.

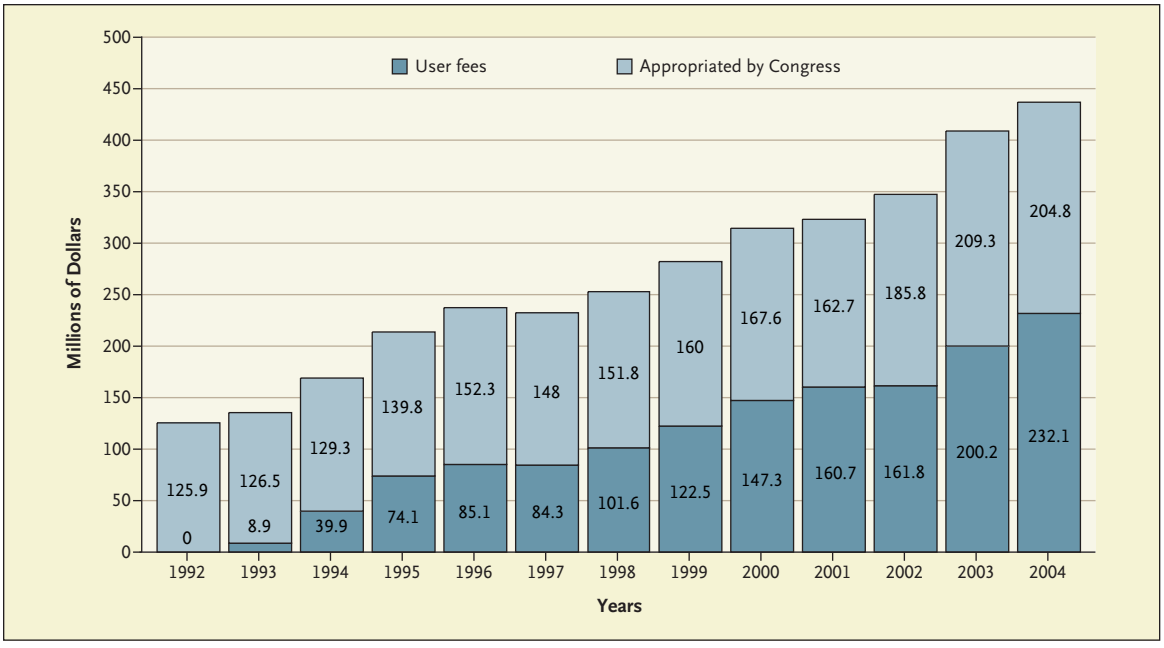
Data are from the Federal Register.

panies' fees (about half a million dollars per drug reviewed) could be spent to evaluate drug side effects after approval — the time when many important safety concerns become apparent. The new law mandated strict deadlines for approval decisions. To comply, the FDA reassigned staff scientists to work on new drug applications, pulling the scientists from other regulatory activities. Several were taken from the Office of Drug Safety, which conducts adverse-effects surveillance — a move that helped to shrink and demoralize that unit.

User fees now account for more than 40% of the budget of the FDA division that reviews new drug applications (see bar graph). Colleagues at the FDA have told me of a worrisome side effect of PDUFA: the growing sense that the organization is accountable to the industry it regulates. One FDA scientist who was often criticized for being too concerned about drug-risk data was told by his supervisor to remember that the agency's client was the pharmaceutical industry. "That's odd," he replied. "I thought our clients were the people of the United States." Other agency staffers report pressure to rush through the drug-approval process, although the FDA's regulatory review times are already among the shortest in the world. Evidence is accumulating that this emphasis on speed may lead to problematic decision making. Data analyzed by Daniel Carpenter, a professor of government at Harvard University, suggest that drugs approved just before PDUFA deadlines are far more likely than those approved at other points in the review cycle to cause safety problems after they are in widespread use.[1]

Most federal regulatory agencies do not derive such a large proportion of their operating budgets from the industries they oversee. Nor is it typical for such relationships to be negotiated so cozily between the government and the trade group representing the industry. Yet the current FDA proposal for PDUFA renewal was developed in concert with the Pharmaceutical and Research Manufacturers of America.[2] No similar influence has been exerted by any other group.

In 2004, the public was shocked to learn that rofecoxib (Vioxx, Merck) could remain in widespread use for 5 years even though the drug nearly doubled the risk of myocardial infarction and stroke. Its withdrawal from the market aroused serious doubts about the adequacy of the FDA's drug-safety surveillance system. Last year, the Institute of Medicine (IOM) and the Government Accountability Office (GAO) released influential reports concluding that the country's capacity for identifying drug risks was greatly in need of repair[3,4]; the IOM report proposed a number of specific and plausible recommendations for reform.



Funding for the FDA's Center for Drug Evaluation and Research.
Data are from the FDA.

By coincidence, this year PDUFA is up for renewal.

For a time, it seemed possible that this combination of forces would lead to concrete steps to build a better system for drug approval and adverse-effects surveillance. But the legislative plans that are likely to be enacted do not even come close to achieving that goal. At a recent meeting on the FDA's future, all four former FDA commissioners in attendance agreed that the agency should be funded directly through the Treasury, rather than through industry payments. But Congress and the agency's leadership still don't get it. The FDA supports reauthorization of PDUFA and proposes that a trivial less than 7% of the user fees be used to strengthen its capacity for adverse-effects surveillance — an amount far short of what would be needed to repair the inadequate system described by the IOM and GAO.

Another key problem may not be fixed by Congress either. The FDA currently lacks the authority to require companies to conduct follow-up studies of suspected safety problems. Most such studies are therefore not performed, even when they are requested (see pie charts). But the requisite legislation to give the agency this vital authority also seems unlikely to emerge from this Congress.

Proponents of retaining PDUFA argue that the discretionary federal budget has been so decimated that it's impossible to find public dollars to replace the $438 million in user-fee revenues projected for 2008. Yet with Medicare now the largest purchaser of drugs in the United States, this is a fiscally irresponsible excuse. Many drug-safety researchers believe, for example, that appropriately conducted studies would have revealed the cardiovascular toxicity of rofecoxib well before the end of its 5-year run. By that point, the country was spending $2.5 billion per year on the drug, about a billion of which was public money. Documenting the drug's risks and getting it off the market just 1 year sooner would have paid for a robust system of drug-safety surveillance for 4 years, without relying on a dime of user fees or additional taxpayer dollars. We spend more than $2 billion on the Iraq war in about a week. A nation as wealthy as ours can afford what it chooses to afford.

The present confluence of events surrounding PDUFA reauthorization could have provided the best opportunity in a generation to act decisively in mending our dysfunctional drug-approval and surveillance system. But Congress, the FDA, and the drug industry risk missing this opportunity. "The train has left the station" is how Capitol staffers describe the inevitable renewal of the plan and the rushed schedule of its legislative trajectory. But that needn't be the case. Recently,

I joined a group of drug-safety experts — several of them former FDA scientists or authors of the IOM drug-safety report — in calling for the FDA's drug-related work to be funded by general federal revenues, rather than by the industry it regulates. We argued that if this change cannot be accomplished before the current user-fee act expires on September 30 (and with it the salaries of many FDA drug reviewers), then PDUFA should be renewed for 6 to 12 months at most, to give the country time to have the debate we deserve over the best way to ensure the efficacy and safety of our medications.[5]

Many in Congress still believe that the user-fee system is saving the public money. That view is as invalid as the smug conclusion of the hospital administrator I spoke with years ago. In regulatory policy, as in grand rounds, there's no such thing as a free lunch.

An interview with Dr. Avorn and Dr. Mark McClellan can be heard at www.nejm.org.

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Drug Safety Reform at the FDA — Pendulum Swing or Systematic Improvement?

Mark McClellan, M.D., Ph.D.

Every 5 or 10 years, Congress enacts major legislation addressing pressing issues at the Food and Drug Administration (FDA). This year, the biggest reforms since at least 1997 are expected. A decade ago, reform was motivated by the perception that the agency wasn't getting new medicines to patients as efficiently as possible. Today, a leading concern is that it isn't protecting the public from drugs' risks as effectively as it might.

A key incident in raising such concern was the 2004 withdrawal by Merck of rofecoxib (Vioxx) because of an apparent increased risk of serious cardiovascular events. The withdrawal came amid questions about the FDA's handling of a possible association between selective serotonin-reuptake inhibitors and suicidal ideation in adolescents. Further concerns were raised about the agency's handling of staff disagreements about these and other drugs. In this context, the FDA sought a review from the Institute of Medicine (IOM).

The IOM's September 2006 report included a broad range of recommendations.[1] Legislators have introduced various proposals reflecting these and other ideas, and the FDA has issued an action plan.[2] Major legislation on drug safety is almost certain to be enacted before fall, as Congress reauthorizes the Prescription Drug User Fee Act (PDUFA), which provides fees from drug manufacturers to cover part of the cost of regulation. This legislation will influence the way safety issues are evaluated and addressed, with important implications for the available information about drugs' risks and benefits and for physician prescribing.

It represents an opportunity to implement a more systematic approach to improving drug safety and effective use, if some challenges can be overcome. Steps intended to enhance safety could also increase costs and reduce ac-