

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 sav-

ing 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.

Dr. Avorn is a professor of medicine at Harvard Medical School and chief of the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital — both in Boston.

1. Carpenter D, Bowers J, Grimmer J, Moffitt S, Nall C, Zucker EJ. Deadline effects in drug regulatory review. Robert Wood Johnson Scholars in Health Policy Research Program, Working Paper Series, February 2007. (Accessed April 5, 2007, at <http://www.>

healthpolicyscholars.org/sub-news/working_papers/working_paper_35.htm.)

2. Food and Drug Administration. Prescription drug user fee act. Fed Regist 2007;72: 1743-53.

3. Drug safety: improvement needed in FDA's postmarket decision-making and oversight process. Washington, DC: Government Accountability Office, 2006. (Document no. GAO-06-402.)

4. Committee on the Assessment of the US Drug Safety System, Baciu A, Stratton K, Burke SP, eds. The future of drug safety: promoting and protecting the health of the public. Washington, DC: National Academies Press, 2006.

5. Angell M, Avorn J, Bingham E, et al. An open letter to Chairman Edward Kennedy and Senator Mike Enzi, Chairman John Dingell and Representative Joe Barton, Members of the Senate Health, Education, Labor and Pensions Committee, Members of House Energy and Commerce Committee. March 14, 2007. (Accessed April 5, 2007, at <http://www.defendingscience.org>.)

Copyright © 2007 Massachusetts Medical Society.

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 en-

acted 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-

cess to beneficial drugs. Moreover, the tools available for learning about drugs and ensuring their effective use have changed enormously since the last time drug-safety legislation was seriously considered. Electronic data on prescription use and patient outcomes are now widely available, and prescribing is influenced by sophisticated drug-utilization-management programs, newer forms of drug coverage including tiered benefits, and extensive Internet resources for consumers.

The elements of proposed FDA reforms fall into four main categories. The first is increasing the resources for drug-safety activities. The IOM noted that the FDA and its Center for Drug Evaluation and Research (CDER) are “severely underfunded” and recommended significantly increasing Congressional appropriations.¹

Such public funds increasingly lag behind user-fee funds, a trend that would continue under the FDA’s proposed user-fee agreement for PDUFA reauthorization. The proposed 29% increase in fees would mean more resources for conducting meetings with drug developers to clarify approval standards and for research on predicting safety problems and patients’ responses to drugs. It would also expand the resources for postmarketing surveillance to \$29.3 million, permitting the hiring of additional personnel and the enhancement of postmarketing capabilities. For fiscal year 2008, total user fees would be nearly \$400 million, accounting for more than 40% of FDA resources for drug regulation.

Seeing the agency as overly dependent on industry funding, some observers propose eliminat-

ing user fees. However, the fees are based on the resources required for reviewing drugs and overseeing their use; they are not tied to FDA decisions. The rate at which drugs have been withdrawn from the market has not increased

One reason drugs may be used for years before risks become evident is that we have no active drug-surveillance system.

since PDUFA was implemented, and the increase in resources has resulted in important public health benefits, including a reduction in drug review time estimated to have saved 180,000 to 310,000 lives.³ Furthermore, specific proposals to reduce dependence on user fees only authorize additional spending — Congress has no plans to actually appropriate the funds for the FDA.

The second category of proposed reform is new authority for the FDA. A bill sponsored by Senators Edward Kennedy (D-MA) and Mike Enzi (R-WY) would formally authorize the agency to use a range of regulatory tools to help assure drug safety. The new authority includes the ability to require special medication guides for patients, restrict which physicians can prescribe a drug, and

impose special requirements for prescribers (e.g., documentation of laboratory testing through FDA-approved monitoring procedures). Because of the burdens on providers and patients, including the potential for restricting access, the FDA has in the past used such tools only rarely, for drugs that have important benefits but also clearly cause serious side effects (e.g., thalidomide).

This authority would be exercised through a required “risk evaluation and mitigation strategy,” which might include measures such as prescribing restrictions, limits on direct-to-consumer marketing, and requirements for postmarketing studies. The risk-management strategy would be monitored and updated over time, and the FDA could impose monetary penalties for noncompliance.

Agency critics believe such steps would strengthen the FDA’s enforcement authority; although the agency can remove drugs from the market for noncompliance with marketing or labeling recommendations, it rarely takes this extreme step. But others counter that the liability and adverse publicity facing companies that fail to act on FDA drug-safety findings already compel compliance. Some also argue that increased reliance on special, drug-by-drug regulatory steps would be burdensome and confusing to physicians and patients, leading to access problems, the substitution of less safe or effective treatments, and medical errors.

A third aspect of reform could help avoid increased costs and reduced access from new drug-by-drug regulation: implementing a fundamentally better system for postmarketing surveillance, with

the development of better risk information based on actual experience with every new drug. Many recent high-profile safety problems have resulted not from the FDA's inadequate authority to regulate drugs on the basis of known risks, but from delays in determining whether suspected adverse events were causally related to drug use.

One key reason drugs may be used for years by millions of patients before risks become evident is that the United States has no active drug-surveillance system. The FDA relies on its Adverse Event Reporting System (AERS), which involves the investigation of "spontaneous" adverse-event reports from health professionals, drug manufacturers, consumers, and others. AERS is important, but even with planned improvements, it captures only a small fraction of adverse events.

With almost all prescriptions now processed electronically, and with the availability of increasingly detailed data on health care utilization and outcomes for insured Americans, we could implement a routine, systematic approach to active population-based drug surveillance that could identify potential safety problems much more effectively and relatively inexpensively.⁴ For example, Richard Platt, a professor of ambulatory care and prevention at Harvard Medical School, has noted that with a (now feasible) data network including information on 100 million patients, a statistically significant "signal" of serious cardiovascular risk could have been detected after less than 3 months of ex-

perience with rofecoxib.⁵ Such an electronic surveillance network would also help in targeting follow-up clinical studies to determine causality when necessary and follow-up actions to influence prescribing.

Finally, the IOM report recommended changes in FDA management practices and safety oversight. The FDA says it is implementing many of these, including new dispute-resolution processes and increased participation of drug-safety and epidemiology experts throughout the review process.² Some agency critics go further, proposing a regulatory entity separate from the pre-marketing review process. Although the IOM panel considered this possibility, it concluded that "achieving a balanced approach to the assessment of risks and benefits would be greatly complicated, or even compromised, if two separate organizations were working in isolation from one another."¹

Although substantial disagreements remain about some aspects of reform, now is the time for Congressional action on drug safety. Several conclusions are clear. First, the FDA needs more resources, and the only feasible way to provide them this year is a combination of greater user fees and the maximum possible increases in federal appropriations. Second, new regulatory authority or organizational changes may help, but the promise of such reforms should be weighed against their potential deleterious effects on access to treatments. Finally, it is possible to implement a much

more systematic approach to postmarket monitoring of drugs and to promoting the effective use of medications, by augmenting FDA resources with the rapidly growing array of electronic resources related to drug use. Such an approach will help to minimize the safety problems and scientific disagreements that accompany prescription drug use when evidence is limited — without pushing the pendulum toward excessive restrictions on access to valuable drugs.

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

Dr. McClellan, who was commissioner of the FDA from November 2002 to March 2004, is a visiting senior fellow at the AEI-Brookings Joint Center for Regulatory Studies, Washington, DC, and is on leave as an associate professor of economics and medicine at Stanford University, Stanford, CA.

1. Committee on the Assessment of the US Drug Safety System, Baciu A, Stratton K, Burke SP, eds. *The future of drug safety: promoting and protecting the health of the public*. Washington, DC: Institute of Medicine, 2006.
2. *The future of drug safety — promoting and protecting the health of the public: FDA's response to the Institute of Medicine's 2006 report*. Rockville, MD: Food and Drug Administration, 2007.
3. Philipson TJ, Berndt ER, Gottschalk AHB, Strobeck MW. *Assessing the safety and the efficacy of the FDA: the case of the Prescription Drug User Fee Acts*. Cambridge, MA: National Bureau of Economic Research, 2005.
4. McClellan M. *Fundamental improvements in drug safety for the 21st century: time for a systematic, electronic infrastructure*. Testimony before the Senate Health, Education, Labor, and Pensions Committee, Washington, DC, March 14, 2007.
5. Platt R. *The future of drug safety — challenges for FDA*. Presented at the Institute of Medicine Forum, Washington, DC, March 12, 2007.

Copyright © 2007 Massachusetts Medical Society.