

# Trouble at the FDA: Can we fix the problems affecting you and your patients?

**W**hile often held in high esteem, the FDA has seen its reputation tarnished in recent years by adverse drug regulation experiences, apparent conflicts of interest, and problems with consistent agency leadership.

## ■ Examples of problems at the FDA

- The COX-2 inhibitor disaster that led to the withdrawal of rofecoxib (Vioxx) from the market due its association with adverse cardiovascular effects; a problem the company may have hidden from physicians and the public through manipulation of research reports.<sup>2</sup>
- The recent addition of black box warnings on selective serotonin reuptake inhibitor (SSRI) labels to warn of a potential association with suicidal behavior in adolescents after publicity that some FDA scientists were prevented from presenting this information to review panels.
- A plea bargain agreement in which Pfizer agreed to pay \$430 million to resolve charges that Warner-Lambert, a company it took over, paid doctors to prescribe gabapentin (Neurontin) for off-label uses including bipolar disorder, attention deficit/hyperactivity disorder, and alcohol withdrawal

seizures. Although physicians can prescribe drugs for whatever reason they choose, pharmaceutical companies are prohibited from promoting drugs for unapproved uses.<sup>3</sup>

■ A lack of strong leadership with acting commissioners leading the agency 3 of the past 5 years. The last permanent commissioner resigned in September 2005 after 2 months in the position amidst accusations that he or his family had financial interests in some of the companies regulated by the agency.<sup>4</sup>

Given these and other negative events in conjunction with the dramatic increase in prescription drug use by Americans—up 60% in the past decade to 3.1 billion prescriptions in 2004 with reports of 375,000 adverse events—it's not surprising that a recent survey showed the public wants a stronger FDA. In fact, two thirds support the creation of an independent oversight panel, 70% want the FDA to improve its gathering and reporting on possible harms of drugs and medical devices after their approval, and many believe that industry has too much influence over agency decisions.<sup>5</sup>

How the FDA performs its job matters very much to physicians, the public, and business. In recent months, outside experts and the FDA itself have proposed changes in how the agency handles new drug

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## The FDA's responsibilities

**T**he Food and Drug Administration (FDA) is responsible for protecting the public health by assuring the safety and efficacy of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation—a list that accounts for at least 20% of consumer spending. It does this on a budget of about \$1.7 billion and 10,000 employees. In comparison, the Department of Agriculture has a budget 50 times larger and a workforce 10 times larger.<sup>1</sup>

approvals that will affect all its stakeholders. Before reviewing those proposals, it's worth understanding how the approval process works.

### ■ Speeding approval of new drugs

In the early 1990s, Congress responded to complaints about the FDA's slow drug approval process, particularly regarding HIV drugs, by passing the Prescription Drug User Fee Act (PDUFA). The law mandated that pharmaceutical companies pay fees to the FDA that were then used by the agency to speed up the approval process by hiring more staff and adhering to a strict timetable for review. The PDUFA accomplished its goal; for instance, priority review drugs had their time to approval drop from a median of 14.9 months in 1993 to 6.7 months in 2003, and standard review drugs went from 27.2 months to 23.1 months during the same period.<sup>6</sup> Ironically, in spite of the quicker approval process, in 2005, pharmaceutical companies had a record low number of FDA drug approvals—only 20 as opposed to 36 in 2004.<sup>7</sup>

As quality improvement experts say, however, you often get exactly the results your system was built for. Thus, it is not surprising that in recent years some FDA scientists have complained of increasing time pressures to perform reviews, increased pressure to approve drugs, and inability to communicate directly with the

companies about the drugs they were reviewing so as to clarify study designs and data analyses.<sup>8</sup>

In addition, many observers believe that having the industry support the FDA budget (about \$300 million/year) presents a potential conflict of interest for the agency, particularly in the current pro-business climate of the Bush administration.

Given these reports as well as the adverse drug safety events that have occurred recently, Congress and independent scientists are now calling for more attention to safety and less focus on the approval timetable.

### ■ How the drug approval process works

Companies obtain FDA approval for human trials after promising results from animal trials. Human trials begin with phase 1 trials, which are small studies looking at safety issues in healthy volunteers. Phase 2 studies are trials of safety and efficacy (how well the drug works) in patients with the target condition. If these prove successful, phase 3 studies are undertaken, which include at least 2 large randomized control trials of safety and efficacy. After these studies, which may involve 2000 to 5000 patients at most, the FDA can grant approval for the drug to be sold to the public.

The agency may require a company to conduct additional post-marketing studies as a condition of drug approval. These so-called phase 4 studies are often designed to identify uncommon adverse events or further investigate a drug's effectiveness. Unfortunately, completion of many of these studies is either significantly delayed or never happens. For instance, as of September 2005, the FDA reported that 65% of the 1231 "post-marketing" studies that companies had pledged to carry out were still pending and that many of these had not even been started.<sup>9</sup>

After the drug is released, the agency may collect post-marketing data on

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**Phase 4 studies, often delayed or neglected altogether, could be mandated**

adverse events and ask the companies to participate in this effort. But no further studies can be required of the company.

Major complaints about phase 3 studies are 1) they are relatively small and often study patients who differ in terms of demographics and extent of disease from those who end up using the medicine; 2) they are placebo-controlled trials rather than comparison trials between the new drug and the current standard therapy; and 3) the FDA increasingly uses surrogate endpoints to judge efficacy, such as tumor shrinkage for cancer drugs or LDL cholesterol decrease for lipid therapy, instead of definitive outcomes like morbidity and mortality. To the extent these surrogate endpoints strongly correlate with major outcomes, this can appropriately speed up the approval process, but the value of surrogate markers is not always clear. These characteristics of phase 3 studies often lead to approval of many “me-too” drugs without the information necessary to decide whether they are better than current standard therapy.

### ■ Deficiencies in using surrogate markers

A particular problem with surrogate markers occurs with the review of higher-priority drugs. For these, the FDA may grant provisional approval on the basis of a surrogate measure of clinical benefit shown in a single, uncontrolled trial as long as the treatment addresses an unmet need for a serious medical illness. In return, the FDA requires the company to complete confirmatory trials in the post-approval period, and may withdraw approval of the drug if no benefit is shown in these phase 4 trials.

However, between 1996 and 2003, only 6 of 23 cancer drugs have gone through such post-marketing trials, and the FDA has not withdrawn approval for any of the 23 drugs. Furthermore, many of these drugs cost thousands of dollars per treatment and have low response rates, yet the FDA has not required companies to better define the target populations for their use.<sup>10</sup>

The problem with using surrogate endpoints in short trials has been demonstrated in cardiovascular medicine with the experience using antiarrhythmics to prevent premature ventricular contractions (later discovered to lead to increased mortality), inotropics to improve ejection fraction (no long-term benefit) and, most recently, with nesiritide (Natreacor) for heart failure. The latter drug was approved based on improved pulmonary-capillary wedge pressure and self-reported improvement in dyspnea. Subsequent research and analyses have shown increased rates of renal failure and death but only after hundreds of millions of dollars worth of treatments.<sup>11</sup>

### ■ Recommendations to make the system work

Given the controversy surrounding the release and marketing of medications that later have shown to cause problems, and given the array of real and perceived conflicts of interest in the approval process, the FDA has proposed establishing a Drug Safety Oversight Board that will include outside experts to review safety issues arising with new applications. Others have argued that such a board should be completely independent of the FDA so as to minimize conflicts of interest and potential agency interference with obtaining necessary information from the companies.

The FDA also recently announced a new rule to overhaul prescription drug labeling, information in package inserts, and some drug reference books. The labels are full of information but much of it is inconsequential or difficult to use for prescribing, and most physicians don't read them. The new labels will list safety warnings, advise how to use the drug and dose it, and advise physicians on what patients should be told about the medication. The goal is to give physicians more useful information to make decisions about drug indications and dosing. While the new rule will not change the patient drug information sheets that pharmacists hand out, it may force consumer

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**Eliminating drug company fees that support new drug reviews will minimize conflicts of interest**

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advertising to make clearer statements about medication risks. Finally, the rule will preempt state liability statutes, which upsets some trial lawyers and politicians.<sup>12</sup>

Outside experts have proposed additional ideas to improve the FDA's work: eliminating the current drug company fees that support new drug reviews to minimize conflicts of interest, mandating post-approval studies to look for uncommon adverse events (phase 4 studies), providing more information on relative efficacy of new drugs compared with current medication treatment and attention to real clinical outcome end points, and prohibiting direct-to-consumer advertising in the first 3 years after a new drug is released.<sup>13</sup>

Considering the turmoil surrounding the FDA's performance right now, it is very possible we will see some of these proposed changes come to pass. Given the importance of prescription medications, these changes will be very relevant to the practices of family physicians and their patients' health.

### REFERENCES

1. Slater E. Today's FDA. *N Engl J Med* 2005; 352:293-297.
2. Curfman GD, Morrissey S, Drazen JM. Expression of concern: Bombardier et al., "Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis," *N Engl J Med* 2000; 343:1520-8. Editorial. *N Engl J Med* 2005; 353:2813-2814.
3. Harris G. Pfizer to pay \$420 million in illegal marketing case. *New York Times*, May 14, 2004.
4. Markel H. Why America needs a strong FDA. *JAMA* 2005; 294:2489-2491.
5. Kaiser Daily Health Policy Report. March 3, 2005. Available at: [www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?hint=3&DR\\_ID=28455](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?hint=3&DR_ID=28455). Accessed on March 10, 2006.
6. Okie S. What ails the FDA. *N Engl J Med* 2005; 352:1063-1066.
7. Berenson A. Drugs in '05: Much promise, little payoff; just 20 new products are approved despite biotechnology's hope. *New York Times*, Jan 11, 2006.
8. FDA's review process for new drug applications. Office of Inspector General. March 2003. Available at: [www.oig.hhs.gov/oei/reports/oei-01-01-00590.pdf](http://www.oig.hhs.gov/oei/reports/oei-01-01-00590.pdf). Accessed on March 10, 2006.
9. 65% of promised drug studies pending. *Washington Post*, March 4, 2006 (AP report)
10. Roberts T, Chabner B. Beyond fast track for drug approvals. *N Engl J Med* 2004; 351:501-505.
11. Topol E. Nesiritide—not verified. *N Engl J Med* 2005; 353:113-116.
12. Harris G. New drug label rule is intended to reduce medical errors. *New York Times*, January 19, 2006.
13. Ray W, Stein CM. Reform of drug regulation—beyond an independent drug-safety board. *N Engl J Med* 2006; 354:194-201.