Institute of Medicine, Congress Seek Solutions to FDA’s Safety Woes Through Reform, Funding

By Joel B. Finkelstein

A n Institute of Medicine report has identified gaping holes in the ability of the U.S. Food and Drug Administration to ensure the safety of new drugs, but experts say the proposals don’t solve possibly the biggest obstacle to safer drugs: inadequate funding.

The IOM’s Committee on the Assessment of the U.S. Drug Safety System released their preliminary findings in September, after a series of public meetings held over 15 months. The report contains recommendations for reforming the center within FDA that is responsible primarily for both drug approval and postmarketing safety monitoring.

“Underlying our 25 recommendations is the fundamental view that the interests of the public are best served when safety and efficacy are considered together. However, factors including, but not limited to, the current organizational culture of the Center for Drug Evaluation and Research (CDER), combined with severe resource constraints and a problematic funding mechanism, have impeded the development of a system that optimally integrates the safety and efficacy assessments along a drug’s life cycle, particularly with regard to safety issues arising postmarketing,” the committee states in the report.

Another factor is a lack of consistent leadership at the top of the agency, according to the committee’s chair, Sheila Burke, R.N.

“The committee believes that turnover and instability in the commissioner’s office leave the agency without effective leadership or the potential to emphasize safety as having high priority in the work of the agency,” she testified before the Senate Health, Education, Labor, and Pension Committee in November. The Senate recently confirmed former National Cancer Institute chief Andrew von Eschenbach, M.D., as FDA’s permanent director. He has been acting head of the agency since September 2005 when Lester Crawford, D.V.M., stepped down 2 months after being confirmed.

“Without stable leadership strongly and visibly committed to drug safety, all other efforts to improve the effectiveness of the agency or position it effectively for the future will be seriously, if not fatally, compromised,” she continued.

The report recommends that the center receive more funding and regulatory authority, as well as rebuild its scientific culture and learn to communicate with the public. Several of the specific recommendations have already been included in legislation that was discussed before the Senate committee just a few days after the November hearing.

That bipartisan bill, cosponsored by Senators Mike Enzi (R-Wyo.) and Edward Kennedy (D-Mass.), would give the FDA greater authority to regulate drugs after they have been approved by making label changes, requiring postmarketing studies, placing limits on direct-to-consumer ads, and restricting their distribution. It would also establish a standardized, interactive database of clinical trials designed to aid public oversight and participation, provide a mechanism to track trial progress, and ensure that the results are made public.

“When new information comes to light that demonstrates previously unknown risks about a drug, the FDA, together with the drug industry and physicians, must be ready and able to take swift, appropriate, and decisive action to ensure patient safety,” Enzi said of the measure.

CDER is already adopting several drug safety–related reforms, including efforts to improve communication, enhance collaboration, provide oversight, and improve scientific partnerships and information infrastructure, the center’s director Steven Galson, M.D., said in a statement.

“I believe the IOM report offers a significant opportunity for CDER to reexamine how we address drug safety. The spirit of the report resonates with many of us, even if some have questions regarding specific recommendations,” he said.

How Much Is Enough?

Some experts have less faith that meaningful change will come from the recommendations.

“The report is going to have little impact,” said Leslie Benet, Ph.D., professor in the department of biopharmaceutical sciences at the University of California in San Francisco. He faults the IOM panel members for failing to include any estimate of how much money the FDA needs to do the job right.

In the report, the panel states that more than half of CDER’s funding comes from user fees, but because of Congressional mandates, most of those fees facilitate rapid drug approval rather than ensure safety. The panel also spends an entire chapter cataloging the causes and effects of the currently inadequate resources devoted to safety considerations but
demurred from providing a recommended dollar amount or percent increase, citing a lack of data.

“To suggest that the FDA people and the Congress are going to get together to talk about how much money is needed for this is nonsense. The FDA people can’t do that. They have to follow the president’s budget. … You really need somebody of some authority to say ‘This is what is needed,’” said Benet, who has served on both IOM and FDA advisory boards.

He also questioned why the panel had ignored proposals to split responsibility for postmarketing safety surveillance from CDER’s approval function. Federal legislation introduced last year would have done just that.

“I strongly believe that it needs to be in the same function, but there are people questioning this. I was disappointed that the report didn’t address that directly,” he said.

**Cancer: A Different Story**

Putting his disappointment aside, Benet said the panel made the right decision in focusing on the need to reform postmarketing monitoring of drug safety.

Although procedures for assessing safety during the preapproval processes need some improvement, Burke noted that the biggest problem with the current system is the seeming assumption that safety data from a clinical trial can readily be translated to the real world.

“Drugs are approved after risk–benefit determinations made by FDA, but those determinations are made on the basis of clinical trials with carefully selected participants and under controlled conditions. The real-life use of drugs is often quite different—a drug tested in a few hundred or thousand people is prescribed and used by millions, often for longer periods and in conjunction with other drugs or supplements,” she said.

Rofecoxib (Vioxx) offers a good example of how the true risk of a drug may not emerge until the postmarketing stage. However, even as safety concerns with the

*continued on page 107*
drug began to emerge, it took more than a year for the company to voluntarily withdraw it. Many of the report’s recommendations revolve around avoiding just such a situation in the future.

But how those changes might apply to cancer treatment is not clear. Unlike other pharmaceuticals, even early-stage cancer drugs are tested in patients, often those with complicated diseases. The setting for postapproval use of the drugs is also unique, said Thomas Roberts, M.D., a senior health care analyst at the investment fund Noonday Asset Management in Charlotte, N.C.

“Unlike a drug such as Vioxx, which would be given to millions of patients by hundreds of thousands of physicians in multiple settings, most cancer drugs will be given by a small group of highly informed specialists who are continuing to conduct clinical trials outside of the approved setting,” said Thomas, who while working as an oncologist at Massachusetts General Hospital published research showing that studies of experimental cancer treatments had grown significantly safer over the previous 10 years. There have been some recent safety problems in cancer drugs, such as the potential heart risks associated with trastuzumab (Herceptin) or imatinib (Gleevec), but in both cases the issue was identified relatively quickly and adjustments were made.

However, the nature of cancer treatment is changing. There are more targeted, less toxic cancer treatments on the horizon. Patients are living longer and, for an increasing population of survivors, cancer is a chronic condition rather than a death sentence, he said.

In the future, postmarketing safety is likely to become a bigger issue in cancer than it has been so far. Currently, the FDA seems to have struck a good balance between the need to expedite development and the need for safe drugs, Thomas said.

“In any effort that goes beyond the current checks, we would need to make sure that that balance is not disturbed.”

© Oxford University Press 2007. DOI: 10.1093/jnci/djk045