have a large effect on uncompensated care, either, because poor people tend not to take advantage of such options and because well-insured people might switch to policies with high deductibles and then find that they cannot pay their bills.

Short of universal coverage, however, a number of policy goals may well be worth pursuing. First, transparency in pricing, financial records, and hospital policies could lead to more consistent practices for reporting and awarding free care and bad debt and to greater accountability. It would be helpful if hospitals distinguished more clearly between the two and if the AHA made hospitals' data available for monitoring purposes. The financial-assistance and collection policies of hospitals could be formalized and made public and could be better coordinated with public programs such as Medicaid. Several groups — including Community Catalyst and the California Hospital Association — have proposed models that appear to balance the rights and needs of low-income patients with the realities of hospital survival.

Second, low-income, uninsured patients ought not to be asked to pay inflated prices. Third, uncompensated care has to be financed somehow, and charitable contributions are generally not sufficient, in part because they are often earmarked for other purposes. Uncompensated-care pools do a reasonably good job of leveling the playing field for hospitals that provide large amounts of free care, but there is some danger that they will be used merely to shore up failing or inefficient hospitals. In addition, programs designed to expand access to specialists who work at hospitals might be cost-effective if they prevented unnecessary hospitalizations. At the federal level, perhaps Medicare should consider changes to the DSH funding formula to ensure that funds reach hospitals with large uninsured populations.

Most hospitals and doctors are surely trying to do the right thing. But serving as a safety net while still functioning as a business is a challenge. Until the country decides to provide health coverage for all residents, the problem of uncompensated care will not go away.

1. Hadley J, Holahan J. Who pays and how much? The cost of caring for the uninsured. Washington, D.C.: Kaiser Commission on Medicaid and the Uninsured, 2003.
2. Gabel J, Claxton G, Holve E, et al. Health benefits in 2003: premiums reach thirteen-year high as employers adopt new forms of cost sharing. Health Aff (Millwood) 2003;22(5):117-26.
3. Tu HT. Rising health costs, medical debt and chronic conditions. Issue brief no. 88. Washington, D.C.: Center for Studying Health System Change, 2004.
4. Overview of uncompensated care: an audio-visual conference event sponsored by the Agency for Healthcare Research and Quality. Washington, D.C.: AHRQ/MedPAC, 2002.
5. Weissman JS, Gaskin DJ, Reuter J. Hospitals' care of uninsured patients during the 1990s: the relation of teaching status and managed care to changes in market share and market concentration. Inquiry 2003;40:84-93.

Safety in Numbers — Monitoring Risk in Approved Drugs

Susan Okie, M.D.

In most cases, when a new drug is approved, almost everything known about its safety in humans is based on the responses of a few thousand people who took it during clinical trials. But once the drug is on the market, the real safety testing gets under way. Within a year or two, the number of people who are exposed to the medication may climb into the millions, especially if the manufacturer promotes it aggressively with television or print advertisements that target consumers. If the drug has a dangerous but rare side effect — for example, liver failure or aplastic anemia — that occurs in fewer than 1 in 1000 patients, that effect will generally be recognized only after the medication is being widely used. Moreover, if the drug increases the incidence of a common condition, such as myocardial infarction, that risk, too, is unlikely to be identified until millions of people have taken the drug. About half the drugs that enter the market have serious adverse effects that are detected only after approval.[1]

And these days, more often than not, Americans are the test population. Fifteen years ago, most new drugs were first approved in other countries. If life-threatening side effects showed up after approval, the products never made it to the U.S. market. Today, because of speedier review of product

Dr. Okie is a contributing editor of the *Journal*.

applications by the Food and Drug Administration (FDA), more than 60 percent of new drugs are approved first in the United States.

That shift is a major reason why drug-policy experts, lawmakers, consumer advocates, and federal officials are all calling for better ways of monitoring drug safety. The best ways to expand and improve the current system will be the focus of a new investigation by the Institute of Medicine.

The urgency of this effort is clear: more Americans are taking prescription medications than ever before. In 2004, pharmacists filled 3.1 billion prescriptions, 60 percent more than a decade earlier. Reports to the FDA of drug-related adverse events have increased correspondingly and now total about 375,000 per year — more than twice as many as a decade ago — even though the agency's current surveillance system is passive, relying on the diligence of drug companies, health care providers, and consumers.

"Given how many people are exposed to drugs, how quickly they're taken up in the population, how many people take multiple drugs . . . we're under no illusions that we have a good postmarket system right now," said deputy FDA commissioner Janet Woodcock.

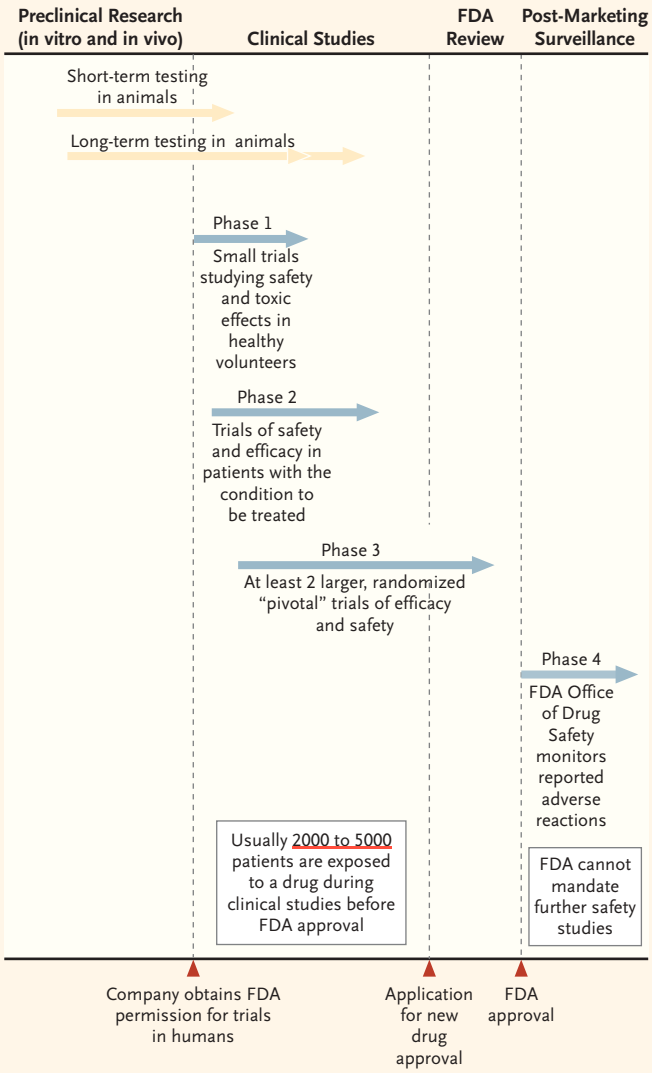
Woodcock and other policy experts suggest that the new system should include ways to gather observational data on large numbers of people who are exposed to medications once they are on the market. Such information might be collected from databases that are increasingly becoming available as managed-care networks and other providers move to the use of electronic medical records.

"The preapproval system is really designed and powered to detect efficacy" rather than safety, according to Alastair J.J. Wood, a professor of medicine and pharmacology at Vanderbilt University School of Medicine, who chaired the recent FDA advisory committee hearing on the safety of cyclooxygenase-2 (COX-2) inhibitors. "That's probably not an inappropriate balance," Wood said in an interview, "but we'd be more comfortable if we had a better postapproval monitoring system." Wood suggests allowing new medications to be marketed with limited FDA approval and then requiring the manufacturer, as a condition of retaining its patent exclusivity, to collect extensive additional data on safety for several years. He favors such an approach over one that severely delays access to new drugs by forcing companies to conduct studies involving tens of thousands of users before approval.

Brian L. Strom, a professor of public health and preventive medicine at the University of Pennsylvania, favors a similar requirement and believes that manufacturers should be prohibited from advertising drugs directly to consumers until the companies have gathered observational data on at least 20,000 users. Consumer-targeted advertising of new drugs tends to boost the number of prescriptions written for patients other than those for whom they are indicated. For example, the explosive growth in sales of rofecoxib (Vioxx) was fueled chiefly by its use for pain due to arthritis in patients who were at low risk for gastrointestinal bleeding and thus could have taken a nonspecific nonsteroidal antiinflammatory drug instead.[2] "Misuse and overuse of new drugs is the central source of much of the problem," said Strom. "The risk–benefit balance for a new drug is much more acceptable if it is used only in the people who need it."

If companies were required to collect safety data after a drug has been marketed, they would be likely to pick up the rare but serious side effects that generally are not identified before approval. Such surveillance would also provide information on the drug's behavior in groups of users, such as the elderly, who tend to be inadequately represented in clinical trials. But if a biologic or epidemiologic signal suggested that a drug might increase the risk of a common disease — as rofecoxib increased the risk of myocardial infarction — then federal regulators would also need the legal authority to require that the manufacturer conduct a randomized, controlled trial to define that potential risk further. Currently, the FDA has no legal power to mandate additional safety studies once a drug has been approved (see diagram). In Europe, by contrast, drug approvals are reviewed again every five years, and pharmaceutical companies pay postmarketing fees that contribute to the cost of safety surveillance.[3]

Bruce M. Psaty, a professor of medicine, epidemiology, and health services at the University of Washington in Seattle, believes that for drugs that patients are likely to take for years, companies should be required to initiate long-term trials before approval and to continue them after the drugs are marketed. "For drugs that are going to be used by millions of people for many years, six-week studies are not adequate to assess the trade-off between risks and benefits," he said. In the case of statins, Psaty pointed out, long-term trials that were completed after approval identified additional, unex-



Outline of the Process of Obtaining FDA Approval for a New Drug.

pected benefits of the drugs. "They expanded the market in ways that helped public health," he said.

As post-marketing surveillance of drugs expands, who should be in charge of minding the safety data? The current system of identifying important risks depends heavily on reporting by pharmaceutical companies, which have a conflict of interest when sifting through adverse-event reports related to their own products. Whistle-blower David J. Graham, an epidemiologist in the FDA's Office of Drug Safety (ODS) who made headlines last fall when he criticized his agency's safety standards, believes that the FDA also has a conflict of interest when it comes to assessing the risks of medications that it has approved. Graham maintains that safety monitoring should therefore be moved out of the FDA. Drug-policy experts outside the federal government are divided on the question of whether a new, separate board or agency is needed.

"To spin off the ODS, I think, would actually be a disaster," said Strom. "Part of the problem now is a lack of communication and coordination" between the review teams responsible for the approval and the labeling of drugs and the ODS epidemiologists who search for drug-related adverse events. The creation of a separate agency could exacerbate that problem, he predicted. Instead, the safety office "needs more people, more resources, and more legal clout."

But Vanderbilt's Wood believes that creating a drug-safety board separate from the FDA, similar to the National Transportation Safety Board, would help to restore public trust and would provide a mechanism for the impartial assessment of risks and the discovery of effective ways to reduce them. If a serious problem developed with an approved medication, the board would conduct an investigation and issue a report. Pharmaceutical companies would face severe penalties if they withheld information about their products from the safety board. "When a plane crashes, we don't turn over the investigation to [the airline] and the air-traffic controllers," Wood said. "We get someone else to do it."

Last month, Health and Human Services Secretary Mike Leavitt and the newly nominated FDA commissioner, Lester Crawford, announced a plan to pursue a middle ground, establishing a new Drug Safety Oversight Board within the FDA that would draw some of its members from inside the agency and some from outside. FDA employees who are involved in reviewing drugs for approval would not serve on the board, which would be free to seek advice from members of the agency's advisory committees and from public-interest groups. Crawford also promised greater openness, saying that the FDA will begin sharing much more of its drug-safety data with the public, even in cases in which such information is considered preliminary. "Our culture, which has received some criticism in past months, is not to alarm the public when we get a signal," he told agency employees. "That era is sort of past. What the public, we think, is demanding is to know as soon as we know what's going on."[4]

It remains to be seen whether the new board will

be truly independent. Senator Charles E. Grassley (R-Iowa), one of the agency's sharpest critics on Capitol Hill, has announced that he will introduce legislation to give the board the authority it needs and has called on Congress to require the registration of all clinical trials.

The changes under way at the FDA are likely to focus public attention on a long-simmering debate within the agency over the level of scientific evidence needed to justify restricting access to a drug or removing it from the market. That tension was evident during the recent advisory committee hearing on COX-2 inhibitors, as panel members and FDA officials wrangled over how to weigh the findings of clinical trials against those of epidemiologic studies in assessing the drugs' cardiovascular risks and deciding whether to allow the drugs to remain on the market.

"Within the agency, the really fierce debates that I remember were when the pharmacoepidemiologists and the clinical-trials folks were in the same room," said former FDA commissioner David A. Kessler. "They're different methodologies. Which one adequately reflects the reality? How much data do you need, and how solid do the data have to be on cause and effect?"

If the Drug Safety Oversight Board functions as advertised, physicians and patients may be able to review the evidence, listen to the debate, and judge for themselves. "The expectations would be that all viewpoints would be represented there," said Wood. "The FDA would be in the happy position of letting it all hang out."

1. FDA drug review: postapproval risks, 1976-85. Washington, D.C.: General Accounting Office, April 1990. (GAO/PEMD-90-15.)
2. Dai C, Stafford RS, Alexander GC. National trends in cyclooxygenase-2 inhibitor use since market release: nonselective diffusion of a selectively cost-effective innovation. Arch Intern Med 2005;165:158-60.
3. Psaty BM, Furberg CD, Ray WA, Weiss NS. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis. JAMA 2004; 292:2622-31.
4. Harris G. F.D.A. moves toward more openness with the public. New York Times. February 20, 2005:A28.

Herbal Medicine in Europe — Relaxing Regulatory Standards

Peter A.G.M. De Smet, Pharm.D., Ph.D.

Herbal medicine is big — and relatively mainstream — business in Europe: in 2003, European countries spent almost $5 billion (at manufacturers' prices to wholesalers) on over-the-counter herbal medicines. But not all European countries have embraced herbal treatments with equal warmth. Germany and France are indisputably in the lead in over-the-counter sales (see graph), and they have also had noteworthy markets for prescription herbal preparations. In 2003, German health insurance paid $283 million in reimbursements for prescribed ginkgo, St. John's wort, mistletoe, saw palmetto, ivy, hawthorn, stinging nettle root, myrtol, phytosterols, and cucurbita, and in 2002, French health insurance paid $91 million in partial reimbursements for ginkgo, saw palmetto, and pygeum prescriptions with a total value of $196 million. Few physicians in the United Kingdom, on the other hand, prescribe herbal medicines, which are generally not covered by the National Health Service, although approximately 1300 herbal practitioners may lawfully sell unlicensed herbal remedies, provided that they do so after consultation with a patient.

Dr. De Smet is from the Scientific Institute of Dutch Pharmacists, The Hague; and the Department of Clinical Pharmacy, University Medical Center St. Radboud, Nijmegen — both in the Netherlands.

Companies that make herbal preparations have usually found it difficult to meet the conventional requirements for proof of medical efficacy, and European countries have also varied in their approaches to this issue. On their own, some countries, such as Germany and France, created simplified registration procedures for herbal products, whereby conclusive evidence of efficacy was no longer required. Other countries, such as the United Kingdom, clung to the principle that industrial herbal preparations should meet the same requirements as conventional medicines, even if this meant that most herbal products could not be licensed and would therefore continue to be sold without firm regulatory control.

The European Community has taken two legis-