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New Painkiller Is Withdrawn After 4 Deaths

By SHERYL GAY STOLBERG

WASHINGTON, June 22— For the second time in two weeks, the Food and Drug Administration has taken the rare step of pulling a prescription drug from pharmacy shelves, a move that is renewing questions about whether the agency's new emphasis on speeding up drug approvals is allowing unsafe medicines to reach patients.

The drug, Duract, a painkiller manufactured by Wyeth-Ayerst Laboratories of St. Davids, Pa., has caused a dozen cases of serious liver failure since it went on the market last July; four patients died and eight required liver transplants. All the cases involved patients who took the drug for longer than the recommended 10 days.

Both the agency and the company are advising patients who have been taking Duract for longer than 10 days to stop immediately; all patients who are using the medication should consult their doctors.

Today's announcement is the third time in nine months that the food and drug agency has removed a new medicine for safety reasons. On June 8, Posicor, a medication for high blood pressure, was banned because it turned out to be potentially lethal when used with a long list of other drugs. Last September, the popular diet drug Redux was taken off the market along with its close cousin, fenfluoramine; both were implicated in heart-valve problems.

"This is the worst record we have ever had; it's unprecedented," said Thomas J. Moore, a senior fellow in health policy at George Washington University Medical Center who studies drug safety. "We are paying the wages of the one-sided debate that we have had in this country that the speed of F.D.A. approval is the only issue."

It is extremely unusual for the F.D.A., which is widely regarded as the most safety-conscious consumer protection agency in the world, to withdraw a drug once it has been approved. Including the most recent withdrawals, there have been only six in the past decade, said Dr. Murray M. Lumpkin, deputy director of the Center for Drug Evaluation and Research at the agency.

In recent years, however, the agency has been under intense pressure from Congressional Republicans to speed its drug approval process; it has given its imprimatur to a record number of new drugs, 92, over the past two years. That fast-track approval process has been financed in large part by the pharmaceutical industry; between 1992 and 1997 the industry paid the F.D.A. $327 million in user fees. The agency used the money to beef up its drug review division, buying new equipment and hiring 600 additional reviewers.

Proponents of the fast-track system argue it is necessary to bring life-saving therapies to patients who desperately need them. But Dr. Lumpkin estimates that only 20 percent of the new medicines approved fall into the category of breakthrough drugs. The rest, including Duract and Posicor, are what is known as "me-too drugs," medicines that treat disorders for which there are already plenty of approved therapies, leaving critics to wonder not only why they were approved in a hurry, but why they are let on the market at all when there is any

"The agency has been put under too much pressure to approve more drugs faster, whether they are needed or not," said Larry D. Sasich, a pharmacist for Public Citizen's Health Research Group, an advocacy organization in Washington. "This is the price that the American public is paying for believing that the F.D.A. was keeping lifesaving medicines out of the hands of the American public, which is simply not true."

Dr. Lumpkin defended the agency, saying the review of Duract took nearly three years and was extremely thorough. Although the agency was aware of the potential for liver problems with long-term use, he said, it made a calculated decision to approve the drug for short-term use, no more than 10 days, reasoning that the benefits outweighed the risks.

"This was not a rushed decision by any means," Dr. Lumpkin said, adding that the agency still believes the drug is safe and effective when used for fewer than 10 days. "There is nothing in our data that makes you think that if you used this product as labeled it would be unsafe."

But Dr. Sasich wondered why the agency approved Duract in the first place, when there are plenty of other drugs on the market to treat pain.

"This was a drug that no one needed," he said. "It's the same scenario as we went through with Posicor."

During the 11 months that Duract was on the market, it was prescribed to 2.5 million people, according to the manufacturer, Wyeth-Ayerst, a division of American Home Products Corporation. Dr. Philip deVane, the company's North American medical director, said 15 percent of the prescriptions were written for longer than 10 days, despite clear warnings on the label.

The drug, which goes by the generic name bromfenac, belongs to a class of medications known as nonsteroidal anti-inflammatory drugs. In addition to treating pain, these drugs, some of which are so safe they can be sold over the counter, are often used for chronic conditions like rheumatoid arthritis. Experts say patients typically take such drugs for weeks or months at a time, which may explain why doctors continued to prescribe Duract for long periods.

Dr. Lumpkin said the long-term and short-term effectiveness of Duract was studied in 2,500 patients before it was approved. When patients in the long-term studies began showing evidence of dangerously elevated liver enzymes, he said, they were taken off the drug. After that, their liver functions returned to normal.

Duract went on the market last July; by February of this year, Dr. deVane said, Wyeth-Ayerst had received three reports of liver injuries to patients who were taking the drug for longer than 10 days. At the F.D.A.'s request, the company then put a black box on Duract packages to highlight the warning against extended use. At the time, no patients had died; Dr. deVane estimated that only one of every 20,000 patients who took Duract suffered serious injury.

But when the food and drug agency continued to receive reports of liver trouble, including the four deaths, Dr. Lumpkin said, officials decided that the risk was no longer worth the benefit.

"When there are other alternatives that don't have this kind of serious reaction over long-term use, there is no reason to take the risk," he said.

The agency asked the manufacturer to withdraw Duract, and Wyeth-Ayerst complied, describing the decision as voluntary.

In both the case of Posicor and Duract, Dr. Lumpkin said, the agency's system for tracking adverse reactions to drugs once they are approved picked up problems that could not be detected in clinical trials, which involve much smaller numbers of people.

"It's the system working; it's not the system not working," he said.

But Mr. Moore, the health analyst at George Washington University, contends that the monitoring system is "extremely weak."

While the agency has 1,400 employees whose primary duties are to approve new drugs, he said, only 52 are assigned to monitor these drugs once they get into the medicine cabinets of consumers. That patients died even after doctors were warned about Duract, he said, is evidence of the system's flaws.

"We have no system to know whether even the safety warning messages we are sending are even being received and heeded by doctors," Mr. Moore said. "We don't even check."