Safety concerns about new drugs revealed

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What's safer: a newly approved drug or one that has been on the market much longer? Newer drugs have a one in three chance of acquiring a black box warning or being withdrawn for safety reasons within 25 years of their approval, according to a new study by researchers from Cambridge Health Alliance /Harvard Medical School, Boston Medical Center (BMC)/Boston University School of Medicine (BUSM), City University of New York School of Public Health, and Public Citizen. The study, published today in the August issue of *Health Affairs*, is the largest on this topic, encompassing all of the drugs approved by the U.S. Food and Drug Administration (FDA) over a 35-year period.

Black box warnings are part of the prescription medication label intended to alert consumers and health care professionals about important safety concerns, such as serious side effects or life-threatening risks. They are the most serious medication warnings required by the FDA.

The study compared warning and withdrawal rates for drugs released before and after 1992. The approval process for medications changed in 1992 with the Prescription Drug User Fee Act (PDUFA), which allowed the FDA to collect fees to expedite drug approvals. Congress passed PDUFA after heavy lobbying by the pharmaceutical industry, and PDUFA has been reauthorized by Congress several times. Since the law's enactment, the average drug approval time for all drugs has fallen from 34 months to 16 months.

Very few of the 32 drugs withdrawn for safety reasons had clearly

unique benefits at the time of approval, but all had unique risks that eventually led to their withdrawal.

The researchers discovered that drugs released after the PDUFA passed were more likely to be withdrawn or have a black box warning, with 26.7 percent of these drugs receiving such a warning compared to 21.2 percent in the pre-PDUFA drugs that underwent the longer approval process. Half of all black box warnings appeared after a drug had been on the market for 12 years, and safety withdrawals have occurred as late as 30 years after a drug's initial release.

The authors suggest that the expedited process may have led to the release of drugs before they could be adequately evaluated for safety issues.

"The FDA is under constant pressure to rush new drugs through the pipeline to approval. In its hurry, the FDA is apparently failing to distinguish useful drugs from toxic ones, and more dangerous drugs are slipping through," said study lead author Cassie Frank, MD, a physician at Cambridge Health Alliance and an instructor in medicine at Harvard Medical School. "By the time many drugs receive serious safety warnings, millions of Americans have already been exposed to their side effects, which can sometimes be fatal. As a doctor, I try to keep my patients safe by avoiding new drugs, when there are similar, older ones available."

"Our findings raise concern that the FDA is rushing its review of new drugs and allowing potentially unsafe medicines onto the market. As a primary care doctor, I'm wary of prescribing brand new drugs unless they're really a breakthrough, since their full risks are often unknown. And patients should be wary too," said senior author Karen Lasser, MD, MPH, associate professor of medicine at BUSM who practices internal medicine at BMC.

"The FDA's resources for reviewing drugs have increased dramatically since the passage of PDUFA, amounting to $760 million this fiscal year from pharmaceutical companies, about two-thirds of the agency's drug review budget," said study co-author Sidney Wolfe, MD, founder of Public Citizen's Health Research Group and author of "Worst Pills, Best Pills." "Since PDUFA, the review times for the drugs that are eventually banned have decreased enormously. From an average, prior to PDUFA, of about three years from receipt of the drug application to FDA approval, the interval has dropped sharply to about one year, following PDUFA. These shorter review times, combined with increased FDA authority to require further studies after approval – rather than settling safety issues before approval – possibly contributes to the increased rate of withdrawals and black box warnings."

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