

# FDA Deadlines May Compromise Drug Safety by Rushing Approval

CAMBRIDGE, Mass. - Many medications are approved by the U.S. Food and Drug Administration on the brink of congressionally mandated deadlines, and those drugs are more likely to face later regulatory intervention than those approved with greater deliberation, researchers at Harvard University have found. Drugs fast-tracked by the FDA are more likely to eventually be withdrawn from global markets for safety reasons, undergo manufacturing revisions, or face labeling changes, according to Daniel Carpenter, professor of government in Harvard's Faculty of Arts and Sciences. The research will be published in the Mar. 27 issue of the *New England Journal of Medicine*.

Carpenter's co-authors were Jerry Avorn, Professor of Medicine at Harvard Medical School/chief, Division of Pharmacoepidemiology at Brigham and Women's Hospital and Evan James Zucker, a student at Harvard Medical School.

"We found that while these deadlines speed up the approval process, many drugs are approved right up against the deadline, which might lead to unintended consequences with regard to drug safety," says Carpenter. "This suggests that drug safety might improve under an FDA approval protocol that is more flexible and less driven by deadline pressures and more by stable growth in FDA resources."

The deadlines imposed on the FDA's drug-approval process were first enacted as part of the Prescription Drug User Fee Act (PDUFA) of 1992, which mandated that the FDA must act on 90 percent of all drug candidates within 12 months of submission or face funding cuts. The timeline was tightened to 10 months as part of the 1997 Food and Drug Administration Modernization Act, a timeline extended by Congress in 2002 as part of bioterrorism legislation and renewed again in 2007.

Some observers have suggested that these deadlines lead to the rushed approval of medications, a theory Carpenter tested by examining data on the timing of FDA approvals dating back to 1950. He found that the enactment of PDUFA in 1992 appeared to introduce a temporal discontinuity into FDA review cycles, with disproportionate approvals coming in the two months immediately before deadlines. Compared to drugs approved at a more measured pace in the months following the

deadline, those approved right before the review clock expired were far more likely to require later regulatory intervention.

“Drugs rushed to approval just before the deadline are two to three times more likely to eventually be pulled off shelves due to safety concerns, two to seven times more likely to receive added label warnings known as ‘black box revisions,’ twice as likely to experience changes in manufacture, and two to seven times more likely to be voluntarily discontinued by manufacturers due to weak clinical demand,” says Carpenter.

In previous work, Carpenter developed a mathematical model to understand how government agencies “learn” and how deadlines affect organizational behavior. This model predicts the pattern of outcomes described in the New England Journal study.

Fifty years ago, the FDA approved most new medications within a few months of receiving applications from manufacturers. Over time, the process slowed as new review protocols were added in the wake of pharmaceutical missteps such as thalidomide, which led to the births of thousands of deformed babies in the late 1950s and early 1960s.

“Because of similarly high-profile regulatory mistakes in recent years, we will likely see greater congressional scrutiny in coming decades as these FDA deadlines come up for renewal every five years,” Carpenter says. “While we are not arguing that these deadlines should be abandoned, our research indicates that mechanisms other than strict deadlines may better balance the need for expeditious yet rigorous drug approval.”

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Source: Harvard University