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OBSERVATIONS

THE WASHINGTON BRIEF

Does $760m a year of industry funding affect the FDA's drug approval process?

A study out this week indicates that new "black box" warnings and safety withdrawals have increased since the drug approval process was changed

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In 1992, because of widespread concern that the US Food and Drug Administration was taking too long to approve drugs, the Prescription Drug User Fee Act (PDUFA) was enacted, authorizing the FDA to collect user fees from drug companies to expedite the approval process. Besides providing funding for an increased FDA staff, the act established performance goals during the approval process to ensure more rapid review.

As of the current fiscal year (October 2013 to September 2014), $760m (£450m; €570m) in drug industry money is allocated to the FDA's Center for Drug Evaluation and Research, comprising a large proportion, more than 60%, of the center's drug review expenditure.[1]

The hypothesis posed in a study published this week was that "new black-box warnings and safety withdrawals have increased following PDUFA's enactment, perhaps as a result of an expedited review process that may not adequately detect serious drug safety problems in the preapproval period." This was the first study to look at all FDA drug approvals for a long enough time before and after the enactment to examine this question.[2]

The study involved the 748 new molecular entity drugs approved by the FDA between 1975 and 2009. The principal finding was that "drugs approved after the act's passage [from 1993 to 2009] were more likely to receive a new black-box warning or be withdrawn than drugs approved before its passage (26.7 per 100.0 drugs versus 21.2 per 100.0 drugs at up to sixteen years of follow-up," a statistically significant 25% increase in the rate of such safety actions.

In the case of drugs withdrawn from the market, the average review time for those approved before PDUFA was around three years, but this had fallen sharply to one year for the post-PDUFA drugs. After PDUFA was passed, the number of approvals of new molecular entity drugs rose dramatically, with 92 approved in 1996 and 1997 combined, considerably more than in any other two year period from 1975 to 2009.[3] Of the 39 new drugs approved in 1997, a fifth (eight) were eventually withdrawn for safety reasons, considerably more than in any year in the 1975 to 2009 interval encompassed by this study.[2] These eight withdrawn drugs were three fluoroquinolone antibiotics, one appetite suppressant, one antidiabetes drug, one statin, one non-steroidal anti-inflammatory drug, and one antihypertensive drug—none arguably breakthrough drugs.

Although the study found that the faster post-PDUFA drug approvals were associated with a higher rate of subsequent safety withdrawals and black box warnings, it could not establish a causal connection between the funding aspects of PDUFA and the increased dangers of these outcomes.

However, coinciding with the original law and its renewal every five years have been legislative changes that often outline specific steps or pathways toward faster drug approval. One such change has given the FDA the authority to mandate post-approval studies to resolve safety issues that have arisen during the pre-approval review of a drug. There is therefore concern that one reason for the outcomes documented in this new study is that the shorter review times—combined with increased FDA authority to require further studies after approval, rather than settling safety issues before approval—have contributed to the increased rate of withdrawals and black box warnings.

In a survey of FDA physicians who review drugs (medical officers) conducted in 1998, by which time the PDUFA effect had clearly sunk in, many of the 53 respondents expressed concern that drugs they thought should not have been approved had been, despite negative safety conclusions. Respondents thought that standards of safety and efficacy had been weakened since the passage of the law. Nineteen medical officers identified a total of 27 approved new drugs in the past three years that they reviewed that they thought should not have been approved. Most of these medical officers said that current FDA standards were "lower" or "much lower" than previous ones. Twelve

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medical officers identified 25 new drugs that they reviewed in the past three years that in their opinion had been approved too fast.[4]

The most important preventive remedy for this post-PDUFA increase in safety withdrawals and black box warnings would be to restore more thorough reviews of the majority of approved drugs that clearly do not represent a therapeutic breakthrough. For the smaller proportion of drugs that appear to represent important advances, a shorter approval time, without compromising standards of safety or efficacy—as occurred in the case of approval of the antiviral zidovudine, a long time before the PDUFA—is appropriate.

But because these much needed changes have not yet occurred at the FDA, the principle of caveat emptor (and caveat prescriber) must be applied. An important conclusion of the new study was that patients should delay using any new non-breakthrough drug until it has been on the market for several years and is thereby less likely to be subject to a safety withdrawal or a new black box warning. An article published several years ago discusses the "seven year rule," referring to the suggestion that in the case of drugs that aren't breakthroughs—the majority of drugs approved—it is safer to wait at least seven years after approval before using them. Even though subsequent withdrawals and new safety warnings beyond seven years will still occur, older alternative drugs are, on average, safer.[5]

The answer to the question in the title of this article seems to be yes, but the source of the impact on the approval process goes beyond the massive drug industry funding itself and is likely to be related to many of the legislative, regulatory, and attitudinal changes that have inevitably accompanied PDUFA and its renewal every five years.

Competing interests: I am a coauthor of the *Health Affairs* article on which this article was based.[2]

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