FDA Drug Review Deadlines: A Safety Concern?

Carpenter D, Zucker EJ, Avorn J. Drug-review deadlines and safety problems. N Engl J Med 2008;358:1354–61.

Study Overview

Objective. To examine whether deadlines imposed by the Prescription Drug User Fee Act (PDUFA) for completion of U.S. Food and Drug Administration (FDA) drug reviews have led to increases in drug safety problems.

Design. Retrospective cohort study.

Data set. All new molecular entities (ie, drugs with a new active ingredient not previously approved in the United States) approved by the FDA between 1950 and 2005.

Main outcome measures. Timing of drug approvals before and after PDUFA was enacted, estimated by Cox proportional-hazards models, and the association between PDUFA deadlines and postmarketing safety problems (ie, withdrawal, black box warnings, dosage-form discontinuation), determined by exact logistic regression.

Main results. Drugs were 3.4 times more likely to be approved in the 2 months before the PDUFA deadline as compared with other times in the review cycle. As compared with drugs approved at other times, drugs approved in the 2 months before the PDUFA deadline were more likely to be withdrawn for safety reasons (odds ratio [OR], 5.5 [95% confidence interval {CI}, 1.3–27.8]), more likely to carry subsequent black box warnings (OR, 4.4 [95% CI, 1.2–20.5]), and more likely to have 1 or more dosage forms voluntarily discontinued by the manufacturer (OR, 3.3 [95% CI, 1.5–7.5]).

Conclusion. Deadlines imposed by PDUFA may lead to the approval of drugs with a higher likelihood of safety problems.

Commentary

Over the past few years, the FDA has withdrawn or issued black box warnings for several high-profile and frequently administered drugs. Carpenter et al examined whether regulatory changes enacted through PDUFA played a role in the recent increase in drug safety warnings issued by the FDA. Their analysis suggests that regulatory changes have impacted drug safety, and they bring new data to a discussion dominated by anecdotes.

Prior to the implementation of PDUFA, drugs could languish in the FDA approval process for up to 3 years due to resource and budgetary constraints that could not accommodate rapid drug approval. In the early 1990s, AIDS activists [1] began to demand faster drug approvals, and the pendulum between safety and access moved further towards quicker patient access to drugs. The enactment of PDUFA allowed for the hiring of more FDA staff, but resources were provided through user fees paid by industry when a drug was submitted for review, and deadlines were imposed on the duration of regulatory review [2,3]. In 1992, when PDUFA was initially implemented, the FDA was required to review and act on 90% of standard new molecular entities within 12 months and 90% of priority new molecular entities within 6 months. By 1997, it was clear that PDUFA was effective, and the average regulatory review period for all molecular entities had been reduced to 1 year [3,4]. However, recent high-profile drug withdrawals suggest that drug safety may have been to some extent sacrificed to ensure more rapid patient access. In response to recent drug safety concerns, Congress enacted new legislation in 2007 that provides more funding to the FDA for drug safety monitoring postapproval and gives new regulatory powers to ask manufacturers for postmarketing clinical trials. Critics suggest that these regulatory changes are necessary but not sufficient [4–6]. Carpenter et al demonstrate that increased postmarketing surveillance may not be enough and a re-examination of the review process itself and the PDUFA-imposed review deadlines may also be necessary.

This analysis is an observational study with the associated limitations. Unmeasured factors may have influenced the observed results; however, Carpenter et al conducted numerous analyses to check the validity of the findings.

Applications for Clinical Practice

Direct-to-consumer advertising as well as detailing to physicians has led to the rapid uptake and use of new medications [5,6]. Regulatory changes to the FDA review process over the past 15 years appear to have affected the relative safety of new medications. When contemplating use of recently approved medications, physicians should weigh the risks and consider prescribing alternatives that have been on the

market longer (and thus have more safety data available) whenever possible.

—Review by Salomeh Keyhani, MD, MPH

References

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