SPECIAL ARTICLE

Drug-Review Deadlines and Safety Problems

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ABSTRACT

BACKGROUND

The Prescription Drug User Fee Act (PDUFA) imposes deadlines for the completion of drug reviews by the Food and Drug Administration (FDA). Critics have suggested that these deadlines may result in rushed approvals and the emergence of unanticipated safety problems once a product is in clinical use.

METHODS

We assessed the association between the PDUFA deadlines and the timing of FDA drug approval by constructing dynamic Cox proportional-hazards models of review times for all new molecular entities approved between 1950 and 2005. To determine whether the deadlines were associated with postmarketing safety problems, we focused on drugs submitted since January 1993, when the deadlines were first imposed. We used exact logistic regression to determine whether drugs approved immediately before the deadlines were associated with a higher rate of postmarketing safety problems (e.g., withdrawals and black-box warnings) than drugs approved at other times.

RESULTS

Initiation of the PDUFA requirements concentrated the number of approval decisions made in the weeks immediately preceding the deadlines. As compared with drugs approved at other times, drugs approved in the 2 months before their PDUFA deadlines were more likely to be withdrawn for safety reasons (odds ratio, 5.5; 95% confidence interval [CI], 1.3 to 27.8), more likely to carry a subsequent black-box warning (odds ratio, 4.4; 95% CI, 1.2 to 20.5), and more likely to have one or more dosage forms voluntarily discontinued by the manufacturer (odds ratio, 3.3; 95% CI, 1.5 to 7.5).

CONCLUSIONS

PDUFA deadlines have appreciably changed the approval decisions of the FDA. Once medications are in clinical use, the discovery of safety problems is more likely for drugs approved immediately before a deadline than for those approved at other times.

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The prescription drug user fee act (PDUFA), originally enacted in 1992, transformed the organization of the Food and Drug Administration (FDA) in several important ways. It was initiated at a time when the FDA was perceived to lack the staff needed to review new drug applications rapidly. Working on the assumption that Congress was unlikely to appropriate additional funds to expand the FDA's staff, the federal government negotiated a plan with the pharmaceutical industry under which drug manufacturers would pay a user fee for each drug review to help cover the costs of the staff required to perform that work. The agreement required the FDA to make a decision on each application within a fixed period after submission.[1,2] Deadlines differed for priority reviews and standard reviews.[3-6]

Critics have argued that the user-fee program makes the agency too dependent on the industry it regulates and has led the FDA to focus disproportionately on the needs of the manufacturers that now fund more than half of its drug-review budget and staff.[7-10] Such criticisms have been heightened by the safety-based withdrawals of rofecoxib (Vioxx, Merck) and valdecoxib (Bextra, Pfizer),[11,12] the delayed recognition of suicidality in children and young adults taking selective serotonin-reuptake inhibitors,[11] and the addition of a black-box warning about congestive heart failure and controversy over the risk of myocardial infarction caused by rosiglitazone (Avandia, GlaxoSmithKline) 8 years after it was approved.[13] A survey[14] and anecdotal reports[9] suggest that FDA scientists perceive the PDUFA as having reduced the agency's focus on drug risks, but there has been no rigorous analysis linking any feature of the user-fee legislation to subsequent safety problems. Some have argued that the PDUFA was successful in speeding the approval of new drugs and found that the overall rate of safety recalls did not increase after its implementation.[6,15]

Many other aspects of drug development and review have also changed since 1992. Review times have probably been accelerated by information technology, submission of higher-quality new drug applications, and patient advocacy. Evaluation of drug safety has also been affected by changes in postmarketing surveillance, knowledge acquired from dealing with previous drug problems, different therapeutic mechanisms, and perhaps a changing culture at the FDA. Therefore, any crude comparison of safety events before and after the PDUFA is not likely to produce valid or revealing answers about its effects. We conducted a quantitative analysis to determine whether a much more specific and plausible mechanism — the deadlines required by the PDUFA legislation — has changed the pattern of FDA decision making, and with what consequences.

METHODS

We used a data set of all new molecular entities (drugs whose active ingredient has never before been approved in the United States) reviewed and approved by the FDA during the period from January 1950 through December 2004.[16] First, we determined whether the user-fee–imposed deadlines changed the pattern of FDA reviews by conducting a dynamic Cox proportional-hazards estimation of review times for all new molecular entities submitted between 1992 and 2005 (313 submissions). The Cox models controlled for the staffing resources of the FDA's drug-reviewing division, and they also included a random-effect term for the product's primary indication. We compared the month-specific timing of approvals for new molecular entities before the enactment of the PDUFA with the pattern of approvals after enactment of the user-fee laws in 1992 and their renewal in 1997. (Cox models were estimated with the use of S-Plus 8.0 software.[17]) The basic estimate reported is that of an approval rate ratio, the likelihood of an approval decision in the 2-month interval before the deadline imposed by the user-fee laws as compared with the likelihood of an approval decision at all other times. We hypothesized that under the PDUFA, approval decisions would be much more likely during the 2 months immediately before the deadline.

We next examined the potential consequences of the PDUFA deadlines. The first implementation of the PDUFA, in 1992 (PDUFA I), required the FDA to review and act on 90% of standard new molecular entities within 12 months and 90% of priority new molecular entities within 6 months. The 1997 renewal of the PDUFA (PDUFA II) required the FDA to review 30% of standard new molecular entities within 10 months by 1997 and to review 90% within 10 months by 2002; the same deadlines continued to apply to priority

entities. The 2002 reauthorization of the law (PDUFA III) maintained the PDUFA II criteria. We compared the rate of postapproval safety problems for drugs approved just before a PDUFA deadline with the rate for drugs approved in other months. The indicators of safety problems that we used included new black-box warnings, withdrawals because of safety problems, and dosage-form discontinuations. In all analyses, we controlled for the number of years the drug was on the U.S. market. Safety-based withdrawals and black-box warnings are the most important indicators of unanticipated postmarketing safety problems.[18]

MEASURES OF POSTMARKETING SAFETY PROBLEMS

Safety-Based Withdrawals

For approved new molecular entities submitted between 1993 and 2004, withdrawals were determined from Scrip reports[19] and Pharmaprojects,[20] which maintain records of all safety-based withdrawals from national pharmaceutical markets. For safety-based withdrawals occurring before 2000, we checked these data against an article by Fung and colleagues.[21]

Black-Box Warnings

For drugs submitted between 1993 and 1999, we used an analysis by Lasser and colleagues to determine whether a black-box warning was added after marketing.[18] For the period from 1999 through 2004, we referred to a listing maintained by the Kansas University Medical Center.[22]

Dosage-Form Discontinuation

A secondary measure was the rate at which dosage forms of the drug were discontinued from clinical use, an action that is often but not always connected with issues of safety. The DrugsatFDA database contains a comprehensive list of drugs approved by the FDA, as well as a list of all changes to a drug's approval package that require an official amendment.[23] For each new molecular entity, we determined whether a dosage-form had ever been discontinued. Because dosage-form discontinuations are not always related to safety or efficacy, we sought to determine whether they were useful markers of safety problems by estimating their association with the other two safety measures — safety-based withdrawals and black-box warnings.

MEASURE OF DEADLINE EFFECTS

For most analyses, we created a composite measure of approval just before the deadline, which indicated whether a drug was a standard new molecular entity approved in the 11th or 12th month of review under PDUFA I, a standard new molecular entity approved in the 9th or 10th month of review under PDUFA III, or a priority new molecular entity approved in the 5th or 6th month under PDUFA I or later user-fee laws. Multiple-cycle reviews (in which the FDA issues what is called an approvable letter on or before the user-fee deadline and asks for a resubmission) were coded as having missed the initial deadline. According to a recent report, 42 (69%) of approvals of new molecular entities from 2002 to 2004 were first-cycle approvals.[24] Using a single variable — the last 2 months before deadline — made it possible to combine the effects of deadlines for different review types and different user-fee requirements.

We first conducted logistic-regression analyses of the postmarketing safety variables as a function of the submission year (time trend), descriptors noting predeadline versus postdeadline approvals, and variables for the drug's primary indication and for its sponsoring firm. We then used exact methods[25] to analyze the same data, using LogXact8 software[26]; more detailed methods and output are reported in the Supplementary Appendix, available with the full text of this article at www.nejm.org.

Using these estimates, we then assessed differences in the risk of postapproval safety problems for drugs approved within 2 months before the PDUFA deadline as compared with drugs approved under three control conditions: all other approved drugs (those approved in all months other than the last 2 months before the deadline), drugs approved in the 2 months after the deadline, and drugs approved well before the deadline (in the first 6 months for a standard new molecular entity and in the first 4 months for a priority entity). Results for all postmarketing safety analyses are reported as odds ratios based on exact logistic regressions.

We considered whether our findings could be confounded by the possibility that drugs approved in the last 2 months before the PDUFA deadlines might be inherently riskier than drugs approved at other times. To assess this possibility, we looked at whether just-before-deadline approval

status was associated with three likely correlates of drug risk: whether the drug was the first in its therapeutic class to be approved, whether the drug was reviewed by an advisory committee before final approval, and the number of hospitalizations per year (per 100,000 population) for the drug's primary indication.

RESULTS

TIMING OF APPROVALS

Figure 1 shows approvals by month for the first 24 months of the review cycle for new molecular entities submitted under the PDUFA and for those submitted during the 30 years before its enactment. For standard new molecular entities (Panel A) and priority entities (Panel D), there was no apparent spike in approval patterns in the pre-PDUFA data. Examining both standard and priority entities submitted from January 1993 to December 2004 with the use of dynamic Cox models, we found that approval was 3.4 times as likely in the 2 months before the user-fee deadline as it was at all other times of the review cycle (95% confidence interval [CI], 2.2 to 5.2; P<0.001); we also found that approvals were 2.7 times as likely in the 2 months before the deadline as in the 2 months afterward (95% CI, 2.0 to 3.8; P<0.001).

RATES OF POSTAPPROVAL SAFETY PROBLEMS

Summary statistics for our measures of postapproval safety problems appear in Table 1, along with a cross-tabulation of the just-before-deadline approval indicator with the postmarketing safety variables. The rates of postapproval safety problems are shown in Figures 2, 3, and 4, which compare the risk of safety problems after just-before-deadline approvals with the risk of problems after approvals at other times; these odds ratios (from exact logistic regressions) are displayed along with their 95% confidence intervals.

The rate at which drug approvals were followed by postmarketing safety problems was significantly higher for products approved in the 2 months before the PDUFA deadlines than for drugs approved at all other times. For approved new molecular entities submitted between January 1993 and December 2004, drugs that were approved just before the deadline had a higher rate of subsequent safety-based withdrawals than drugs approved in other months of the review cycle (odds ratio, 5.5; 95% CI, 1.3 to 27.8; P=0.02). Just-before-deadline approvals were more likely to be followed by assignment of a black-box warning (odds ratio, 4.4; 95% CI, 1.2 to 20.5; P=0.02) or discontinuation of at least one dosage form (odds ratio, 3.3; 95% CI, 1.5 to 7.5; P=0.003) than were other approvals. Such discontinuations had a high positive correlation with safety-based market withdrawals over the past 15 years (odds ratio, 13.9; 95% CI, 3.3 to 69.1; P<0.001) and a positive correlation with the addition of a black-box warning to a drug's label (odds ratio, 4.6; 95% CI, 0.9 to 19.7; P=0.06).

We found a similar postmarketing safety pattern for the comparison of just-before-deadline approvals with approvals made just after the deadline (Fig. 3). As compared with drugs approved after the deadline, those approved just before the deadline were more likely to be withdrawn from the market for safety reasons (odds ratio, 5.7; 95% CI, 1.2 to 37.6; P=0.03), more likely to have a black-box warning added after marketing (odds ratio, 4.0; 95% CI, 1.3 to 16.7; P=0.01), more likely to have one or both of these outcomes (odds ratio, 3.9; 95% CI, 1.3 to 13.1; P=0.01), and more likely to have at least one dosage form discontinued (odds ratio, 3.3; 95% CI, 1.4 to 8.1; P=0.005).

COMPARISON WITH EARLY APPROVALS

We also compared the rates of postmarketing safety problems for just-before-deadline approvals with the rates for drugs approved well in advance of the PDUFA deadlines (within 6 months after submission for standard new molecular entities and within 4 months after submission for priority entities) (Fig. 4). As compared with drugs approved well before the deadline, those approved just before the deadline were more likely to be withdrawn for safety problems (odds ratio, 5.3; 95% CI, 1.3 to 26.5; P=0.005) and more likely to have at least one dosage form discontinued (odds ratio, 3.3; 95% CI, 1.4 to 7.7; P=0.003). Drugs approved just before the deadline were also more likely to have a black-box warning added subsequently, but the odds ratio was not significant (4.4; 95% CI, 0.9 to 28.4; P=0.07). In addition, just-before-deadline approvals were more likely than early approvals to be followed by withdrawal of the drug from the market, assignment of a

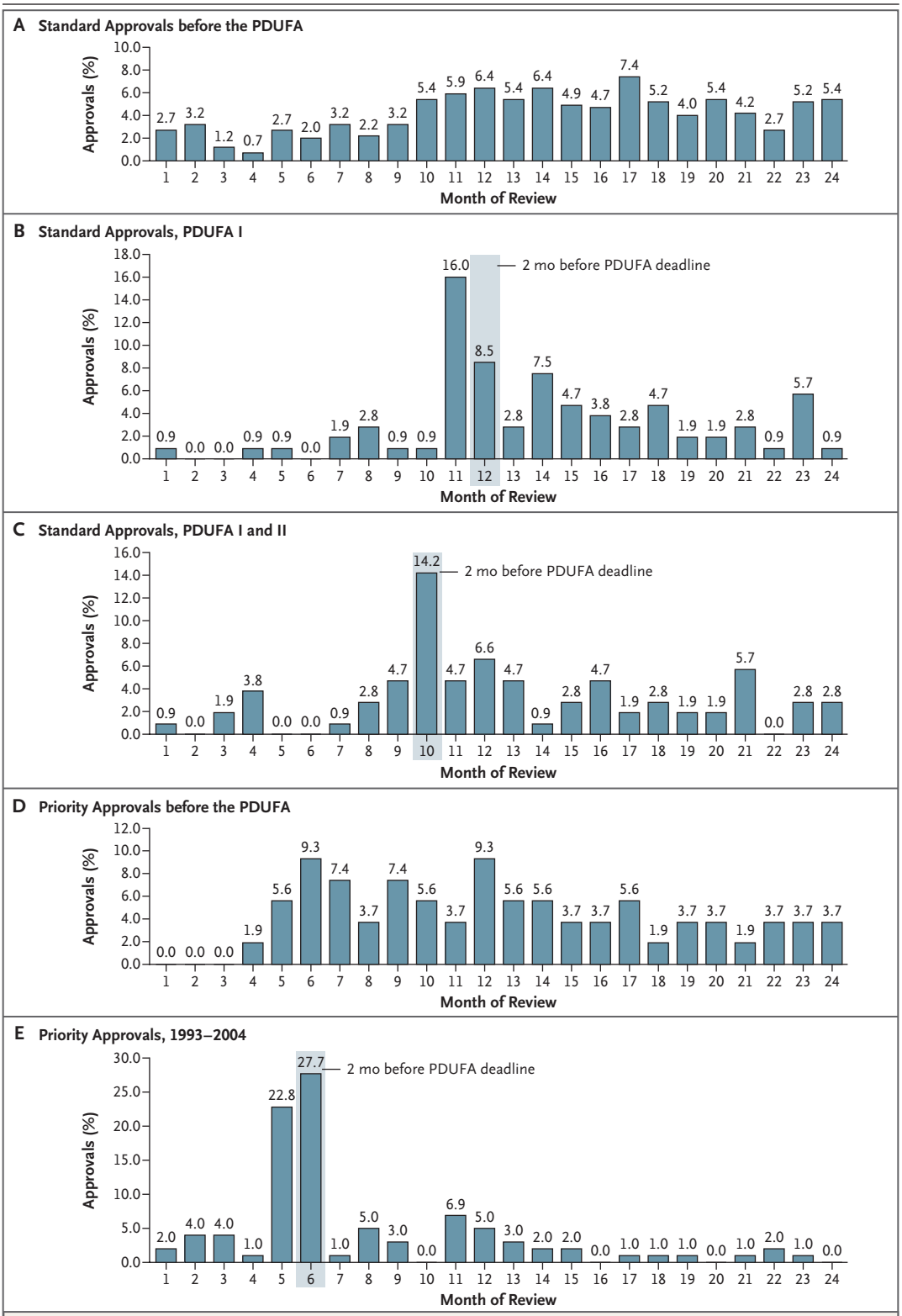

Figure 1. Distribution of Approvals According to Month of Review Cycle before and after Implementation of the Prescription Drug User Fee Act (PDUFA).

PDUFA I set the review deadline for new molecular entities (NMEs) at 12 months for standard NMEs and at 6 months for priority NMEs. PDUFA II set the review deadline at 10 months for standard NMEs and at 6 months for priority NMEs.

Table 1. Safety-Related Events for Drugs Approved Just before the Review Deadline and for Drugs Approved at Any Other Time in the Review Process, 1993–2004.*

Safety-Related Event	Just-before-Deadline Approvals (N=97)	All Other Approvals (N=216)	P Value
	no. (%)		
Safety-based withdrawal			0.04
No	90 (93)	212 (98.1)	
Yes	7 (7)	4 (1.9)	
Black-box warning			0.002
No	87 (90)	212 (98.1)	
Yes	10 (10)	4 (1.9)	
Withdrawal, black-box warning, or both			0.001
Neither	83 (86)	209 (96.8)	
Either or both	14 (14)	7 (3.2)	
Dosage-form discontinuation			0.01
None	72 (80)	187 (91.2)	
At least one	18 (20)	18 (8.8)	

* The total number of approvals evaluated was 313 for all safety-related events except dosage-form discontinuation; for this measure, 295 approvals were evaluated because the new-drug-application (NDA) numbers did not match the DrugsatFDA NDA supplement records for 18 new molecular entities. If the absence of a match is assumed to reflect the absence of a dosage-form discontinuation, the substantive findings are similar (P=0.01).

black-box warning, or both (odds ratio, 4.3; 95% CI, 1.3 to 15.0; P=0.01). In other analyses (see the Supplementary Appendix), we found no evidence for a relationship between the duration of the review itself and postmarketing safety problems; including the approval time as a linear regressor did not result in any significant relationships (P>0.3 for all comparisons).

CORRELATES OF DRUG RISK

We found no evidence of significant associations between the timing of approval and correlates of drug risk. As compared with drugs approved at other times, those approved just before the deadline were not more likely to have first-in-class status (odds ratio, 0.9; 95% CI, 0.4 to 2.3; P=0.90),[16] to undergo review by a premarketing advisory committee (odds ratio, 1.4; 95% CI, 0.8 to 2.4; P=0.29),[27] or to be associated with high hospitalization rates for the primary indication (odds ratio, 1.0; 95% CI, 0.9 to 1.2; P=0.69).[28] These results suggest that drugs approved immediately before the PDUFA deadlines were not inherently more risky than those approved at other times.

DISCUSSION

After 1992, when the PDUFA was passed and deadlines for drug approvals were introduced, FDA drug approval decisions were concentrated in the 2 months just before the deadlines. For drugs approved since January 1993, we found that approvals made in the last 2 months before a deadline were more likely to be associated with subsequent safety problems than were approvals made at other times. This difference was seen when just-before-deadline approvals were compared with just-after-deadline approvals as well as with early approvals (those made 3 months or more before a deadline). As noted in two major reports of deficits in the FDA's capacity for postmarketing safety surveillance,[29,30] ongoing assessments of drug risk are not conducted systematically. As a result, if a safety problem is not detected during the initial preapproval evaluation, it may not be fully defined or included as a prominent warning for years afterward, as occurred with the risks of potentially fatal drug–drug interactions with mibefradil (Posicor, Roche)

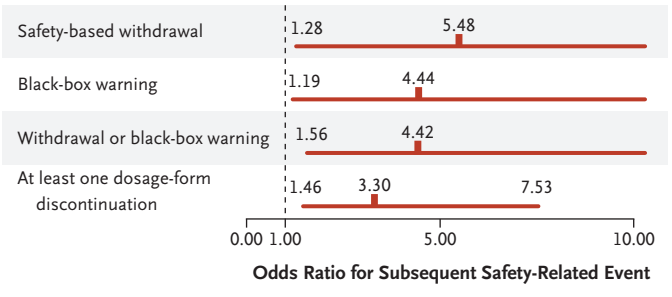

Figure 2. Likelihood of Subsequent Safety-Related Problem for Drugs Approved in the Last 2 Months before the Review Deadline as Compared with All Other Drugs, 1993–2004.

The bars indicate odds ratios, and the horizontal lines 95% confidence intervals.

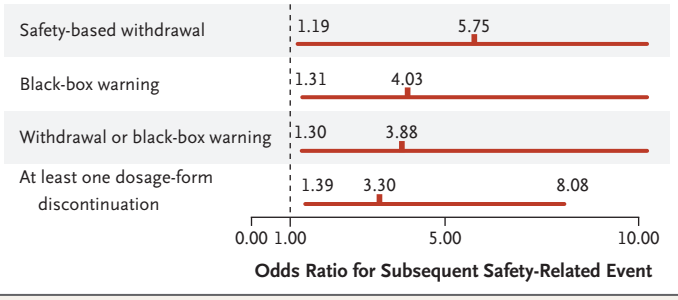

Figure 3. Likelihood of Subsequent Safety-Related Problem for Drugs Approved in the Last 2 Months before the Review Deadline as Compared with Drugs Approved in the 2 Months after the Deadline, 1993–2004.

The bars indicate odds ratios, and the horizontal lines 95% confidence intervals.

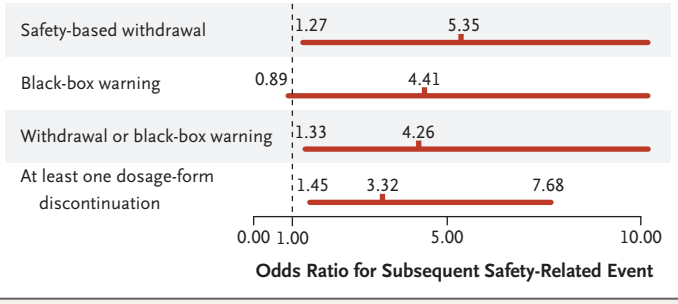

Figure 4. Likelihood of Subsequent Safety-Related Event for Drugs Approved in the Last 2 Months before the Review Deadline as Compared with Drugs Approved in the First 6 Months (for Standard New Molecular Entities) and the First 4 Months (for Priority New Molecular Entities) before the Deadline, 1993–2004.

The bars indicate odds ratios, and the horizontal lines 95% confidence intervals.

and terfenadine (Seldane, Hoechst Marion Roussel), myocardial infarction or stroke with rofecoxib (Vioxx), hepatotoxicity with troglitazone (Rezulin, Warner-Lambert), and rhabdomyolysis with cerivastatin (Baycol, Bayer AG).

Our findings are not consistent with analyses that compared safety problems before and after enactment of the PDUFA and showed no increase in problems after the user-fee system was introduced.[6,15] One potential explanation for the inconsistency is that our analyses explored the law's specific mechanisms instead of making blanket comparisons of all drugs approved before enactment and all those approved after enactment. Although our analysis corroborates other research suggesting that the PDUFA's acceleration of drug-review times was influenced by the incentives it provides for acceleration of drug review,[2] a previous study has shown that the main factor accounting for accelerated approval times was the availability of more staff at the FDA; greater resources made it possible to hire more staff, and approval times were already falling rapidly in the years before the PDUFA.[31] Approvals earlier in the review cycle were not inherently more likely to lead to postmarketing safety problems; it appears to be the deadline, not the speed of approval, that explains the difference in the risk of such problems.

This analysis has all the limitations of observational studies. In particular, approval times were not assigned randomly to drugs, and we cannot rule out the possibility that some unobserved factor was associated with both just-before-deadline reviews and postmarketing safety problems. We have, however, implemented extensive multivariate controls and performed numerous other checks on our analyses (see the Supplementary Appendix).

Finally, we have not conducted a cost–benefit analysis of the legislation, nor have we systematically measured whether the public health burden of subsequent safety problems outweighs the benefits of the user-fee act in accelerating drug review.

Taken together, these findings suggest potential adverse effects of the deadlines governing FDA drug review. There are many ways to accelerate regulatory processes, most notably by providing more staff, which can be accomplished as readily by appropriations as by user fees.[31] Deadlines

may offer a blunt tool with which to accelerate review. But in keeping with reports from FDA scientists,[14,32] our findings suggest that deadlines may also cause drugs approved under these constraints to have a higher likelihood of unanticipated safety problems once they are in widespread use. A plausible hypothesis is that relying more on staffing and less on deadlines could result in the same degree of review efficiency without increasing the risk (and resulting greater cost) of unanticipated drug-safety problems.

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CORRECTION

Drug-Review Deadlines and Safety Problems

To the Editor: Carpenter et al. (March 27 issue)[1] report that new molecular entities (NMEs) approved in the 2 months before the first review deadlines established under the Prescription Drug User Fee Act (PDUFA) showed a higher rate of postmarketing safety problems — as measured by safety-based withdrawals, new black-box warnings, or dosage-form discontinuations — than drugs approved at any other time. They suggest that pressure to respond within the allotted time leads to poorer decision making. We consider the questions they raise to be important and have tried to replicate their analysis of safety-based withdrawals and new black-box warnings. In trying to replicate their analysis, using their definitions but with data from the Food and Drug Administration (FDA), we obtained different counts of drugs approved just before deadline as compared with those approved at other times for reviews classified as priority versus standard, for rates of drug withdrawal, and for black-box warnings. These differences may substantially affect the results of an analysis such as theirs.

PDUFA review deadlines are different for priority drugs (drugs that represent substantial improvements over marketed products) and standard drugs. On the basis of charts provided in their article, it appears that the authors classified 101 approvals as priority and 212 as standard during the PDUFA period they included in the analysis. FDA data show 132 priority approvals and 182 standard approvals. Figures 1B, 1C, and 1E of their article also suggest that 25 standard NMEs were approved before month 10, whereas FDA data show only 4 such approvals. A list of the drugs and deadline classifications used in their analysis would help pinpoint discrepancies between their data and ours. We are providing the FDA data[2] to help identify those differences.

In trying to replicate their analysis of safety-related events for drugs approved just before deadline versus all other drugs approved using FDA data, we found major differences in rates of safety withdrawals and black-box warnings. The authors reported that of 11 safety-based withdrawals for drugs approved during the PDUFA period, 7 were approved just before deadline; according to FDA data, only 5 of 11 drugs meet the authors' definition of just-before-deadline approvals. Carpenter et al.'s analysis cites 14 black-box warnings; the FDA's database of postmarketing black-box warnings lists 29 NMEs with warnings added after approval.

The analysis using FDA data is summarized in Table 1. The FDA data show a somewhat greater rate of withdrawals and new black-box warnings in the just-before-deadline approvals than in approvals for all other drugs, but the difference is small, is not statistically significant, and could easily represent a chance finding. The black-box warnings are most common among priority drugs approved during the first cycle, including drugs for human immunodeficiency virus infection, AIDS, and other life-threatening conditions, for which greater safety risks may be accepted and for which approvals may be based on more limited data.

Table 1. Approved New Molecular Entities (NMEs) for Which Applications Were Received between January 1, 1993, and December 31, 2004.

Table 1. Approved New Molecular Entities (NMEs) for Which Applications Were Received between January 1, 1993, and December 31, 2004.*

Approvals	No. of NMEs	Safety-Based Withdrawal				Black-Box Warning			
		Yes	No	%	P Value	Yes	No	%	P Value
Carpenter et al.									
Total	313	11			0.04	14			0.002
Just before deadline	97	7	90	7.2		10	87	10.3	
All others	216	4	212	1.9		4	212	1.9	
FDA									
Total	314	11			0.19	29			0.40
Just before deadline	88	5	83	5.7		10	78	11.4	
All others	226	6	220	2.7		19	207	8.4	

* Food and Drug Administration (FDA) analyses include safety-based withdrawals and postmarketing new black-box warnings through 2007. While the FDA and Carpenter et al. both cite 11 safety withdrawals in their data, it is not clear if these refer to the same 11 drugs. We cannot replicate the black-box warning counts in this study, so we are using the 29 first-time introductions of black-box warnings per FDA data. "Just before deadline" is defined as first-cycle approval in month 5 or month 6 for priority NMEs, month 11 or month 12 for standard Prescription Drug User Fee Act (PDUFA) I NMEs, or month 9 or month 10 for standard PDUFA II–III NMEs. P values are based on Fisher's exact tests.

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2. Food and Drug Administration. FDA data on PDUFA drug approvals, safety withdrawals and new boxed warnings. (Accessed June 13, 2008, at http://www.fda.gov/oc/pdufa/FDADrugAppSafetyData_files/NMESafetySumm.html.)

The authors reply: In response to Nardinelli et al., my colleagues and I have conducted extensive investigations into the differences between our data and theirs.[1] We identified several errors in our data set. We included five drugs that were not NMEs and excluded six others that were. We coded 35 priority NMEs as undergoing standard review schedules. Our corrected data set includes 132 drugs that underwent priority review. Our original data set on black-box warnings omitted five drugs that had warnings added to labeling before July 2005, when our database was locked. Three others were listed as having a black-box warning added, although these additions did not impart substantial new safety information. I regret the errors. We corrected these errors in our data set (see the Supplementary Appendix, available with the full text of this letter at www.nejm.org), and reanalyzed the corrected data. Our analyses of the corrected data continue to show significant associations between just-before-deadline approval, safety-based withdrawals, and black-box warnings (Table 1, first section).

The differences between the number classified by us and that classified by Nardinelli et al. as being approved just before deadlines do not reflect errors in our data set but were the result of our intentional rounding of numbers such that drugs approved within 2 weeks of the deadline's expiration were classified as having been approved just before deadline. When we reanalyzed our data without rounding, the results were similar (Table 1, second section). Of note, the information posted by Nardinelli et al. is a new data set never before published. It differs significantly from data posted elsewhere on the FDA Web site, from data that the agency has published, and from other published medical literature.[1]

There is a large difference in the number of black-box warnings in our data set and that in the set from Nardinelli et al., but most of this difference stems from the different time frames used in the two analyses. We included black-box warnings issued through July 2005; 17 of the 29 drugs with black-box warnings (58%) included by Nardinelli et al. were added between 2005 and 2007. In addition to the differences resulting from the different time windows, we believe that both our analysis and that by Nardinelli et al. omitted postmarketing black-box warnings, and we have corrected our data set to account for this (see the Supplementary Appendix). When we reanalyzed our corrected data set, with the addition of data through December 2007, we found more modest but still significant associations between just-before-deadline approvals and safety problems (odds ratios, 2.1 to 3.6) (Table 1, third section).

The difference in the results of our analyses of data through December 2007 and the analyses of Nardinelli et al. can be accounted for by their omission of two ofloxacin antibiotics from the safety-based withdrawal count and by their omission of five drugs (adefovir, emtricitabine, entecavir, tenofovir, and tipranavir) from the new black-box warning count. In these cases, drugs with a black-box warning at the time of approval were subsequently relabeled and important safety information and new content were added to the warning.[2]

Table 1. Reanalysis of Data.

Table 1. Reanalysis of Data.*

Approvals	No. of NMEs	Safety-Based Withdrawal					Postmarketing Black-Box Warning					Safety-Based Withdrawal or Black-Box Warning				
		Yes	No	Exact Logistic Regression OR	Exact Logistic Regression P value	Fisher's Exact P Value	Yes	No	Exact Logistic Regression OR	Exact Logistic Regression P value	Fisher's Exact P Value	Yes	No	Exact Logistic Regression OR	Exact Logistic Regression P value	Fisher's Exact P Value
Reanalysis of now data set after correcting for coding and misclassification errors																
Total	314	11	303	4.88	0.04	0.03	19	295	2.85	0.04	0.05	25	289	2.96	0.02	0.02
Just before deadline	97	7	90				10	87				13	84			
All others	217	4	213				9	208				12	205			
Reanalysis of new data without rounding times in classifying just-before-deadline approvals																
Total	314	11	303	5.89	0.01	0.01	19	295	3.41	0.03	0.02	25	289	3.58	0.009	0.006
Just before deadline	88	7	81				10	78				13	75			
All others	226	4	222				9	217				12	214			
Reanalysis of new data, including data through December 2007†																
Total	314	12	302	3.57	0.05	0.06	34	280	2.13	0.048	0.07	40	274	2.24	0.02	0.03
Just before deadline	97	7	90				16	81				19	78			
All others	217	5	212				18	199				21	196			

* The P value for the deadline approval variable was calculated with exact logistic regression controls for submission year, as in the article by Carpenter et al. (For regressions with more controls, see investigative details.[1]) The P value calculated with Fisher's exact test is based on uncontrolled, two-way cross-tabulation, as in the letter from Nardinelli et al. OR denotes odds ratio.
† The P values in this section of the table were all less than 0.05 when rounding was not performed in classifying deadline approvals.

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