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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

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.

providing the FDA data² 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.

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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

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	OR P value	Yes	No	OR P value	Yes	No	OR P value						
Reanalysis of new 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.†) 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.

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

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1. Difference between Carpenter/Zucker/Avorn data and Nardinelli et al data, and re-analysis of data adjusting for these differences, and robustness and sensitivity checks on analyses. Investigations details. May 2008 (memorandum). (Accessed June 13, 2008, at <http://people.hmdc.harvard.edu/~dcarpent/fdaproject/nejmresponse20080517.pdf>)
2. Section 8. Coding of black-box warnings. (Accessed June 13, 2008, at <http://people.hmdc.harvard.edu/~dcarpent/fdaproject/nejmresponse20080517.pdf>)

Hydroxyurea for Sickle Cell Anemia

TO THE EDITOR: In her article on hydroxyurea for the treatment of sickle cell anemia, Platt (March 27 issue)¹ states that “the red cells of a normal adult generally contain almost 100% hemoglobin A and those of a person with sickle cell anemia contain almost 100% sickle hemoglobin.” This statement is not entirely accurate. In the normal adult, hemoglobin A constitutes about 97% of the total hemoglobin, hemoglobin A₂ constitutes about 2%, and hemoglobin F constitutes about 1%.²

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TO THE EDITOR: Platt highlights the use of hydroxyurea in patients with sickle cell anemia who experience vaso-occlusive crises or acute chest syndrome. She notes that “a large number of eligible patients do not have access to this therapy.” Besides limited access to care, this situation could be related to the potentially serious adverse reactions to hydroxyurea, including reproductive side effects, myelosuppression, and the risk of cancer. However, it appears that compliance with

treatment is frequently suboptimal because of the aesthetic consequences of the neglected “minor” cutaneous side effects. These side effects consist mainly of cutaneous hyperpigmentation, alopecia, xerosis, nail pigmentation (longitudinal bands), and leg ulcers.^{1,2} Therefore, to optimize adherence, it is important to systematically inform patients of these reversible adverse effects before initiating treatment with hydroxyurea.

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THE AUTHOR REPLIES: Naina and Harris correctly point out that given the typical amounts of hemoglobins A₂ and F in the adult erythrocyte, it is more precise to describe the amount of hemoglobin A as approximately 97% rather than “generally . . . almost 100%.”

Bachmeyer and colleagues appropriately note the possible adverse effects of hydroxyurea therapy on the skin and consider the potential for those effects to reduce adherence to treatment. As reported in an article that they cite¹ and in