

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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

# Online Appendix for “User-Fee Drug Review Deadlines and the Risk of Subsequent Safety Problems,” NEJM MS 07-06341.

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This paper serves as a technical companion to NEJM 07-06341. We present four sets of results here.

I. Statistical Decomposition of the FDA Review Cycle Before and After PDUFA, including an analysis that suggests why a two-month pre-deadline interval was used in the analysis of postmarket safety problems.

II. Analyses of Postmarket Safety Problems including Random Effects for Drug Primary Indication, Fixed Effects for Sponsoring Firms, and Other Controls.

III. Analyses using the NDA Approval Time itself as a Regressor.

IV. Analyses of Postmarket Safety Problems Using Alternative Windows for Just-Before-Deadline Status.

## I. Statistical Decomposition

We begin by presenting month-by-month estimates of the relative risk of approval, derived from the dynamic Cox models we estimated. Further details on the methodology used can be provided by the authors and can be gleaned from Therneau and Grambsch (reference [17]). Figures 1 and 2 of this Online-Only Appendix show the relative risk of approval, by month of review cycle. (Figure 1 of the paper shows the distribution of approvals over months of the review cycle for NMEs submitted January 1992 to December 2004.) Figure 1 shows three panels, all of which apply only to standard (non-priority) drugs. The first (top) panel of Figure 1 displays relative risks of approval by month before there were user-fee deadlines. The second panel displays relative risks by month under the first set of user-fee deadlines for standard drugs (PDUFA I), when the deadline was set at twelve (12) months. The third (lowest) panel of Figure 1 displays relative risks for drugs submitted under the second set of deadlines for standard drugs (PDUFA II and afterwards), where the deadline was ten (10) months.

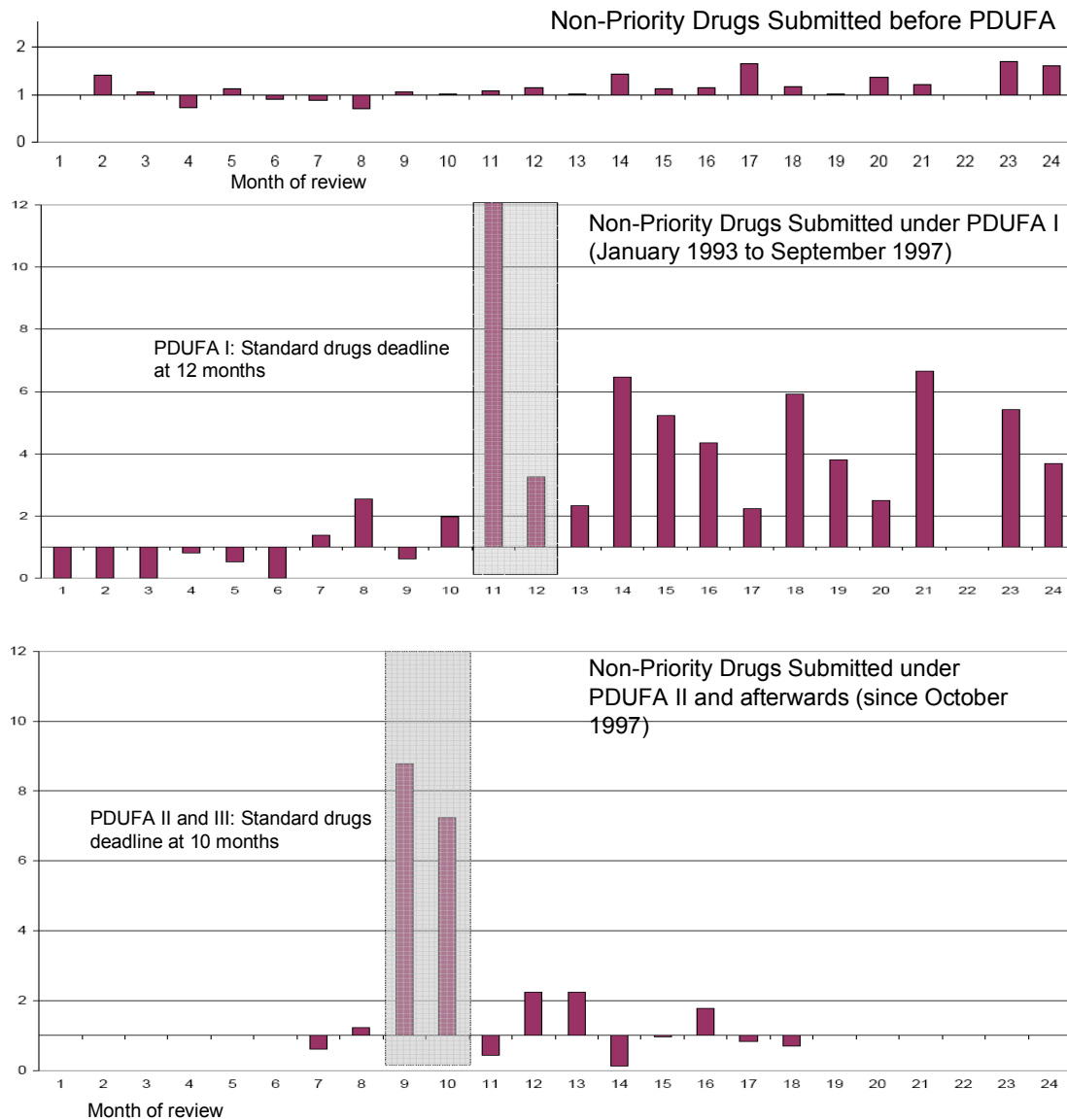
Figure Two displays the same month-by-month relative risks of approval, but for priority drugs.

These figures demonstrate why the two-month window is superior to other plausible windows (such as one months or three months, for example). For instance, in no case do we observe a statistically significant or sizable jump in approval risks in the third month before a PDUFA deadline. (This would be the tenth month of the PDUFA schedule for standard NMEs, where the deadline was twelve months; the eighth month of the FDAMA

schedule for standard NMEs, where the deadline was ten months, or the fourth month of the schedule for priority NMEs, where the deadline has remained at six months since 1992.)

The largest relative risks that are statistically significant occur in the second month before the deadline. This is the eleventh month of the PDUFA schedule for standard NMEs, the ninth month of the FDAMA schedule for standard NMEs, and the fifth month of the schedule for priority NMEs. This suggests that using a one-month window would also misrepresent the FDA's review behavior in the aftermath of the PDUFA law.

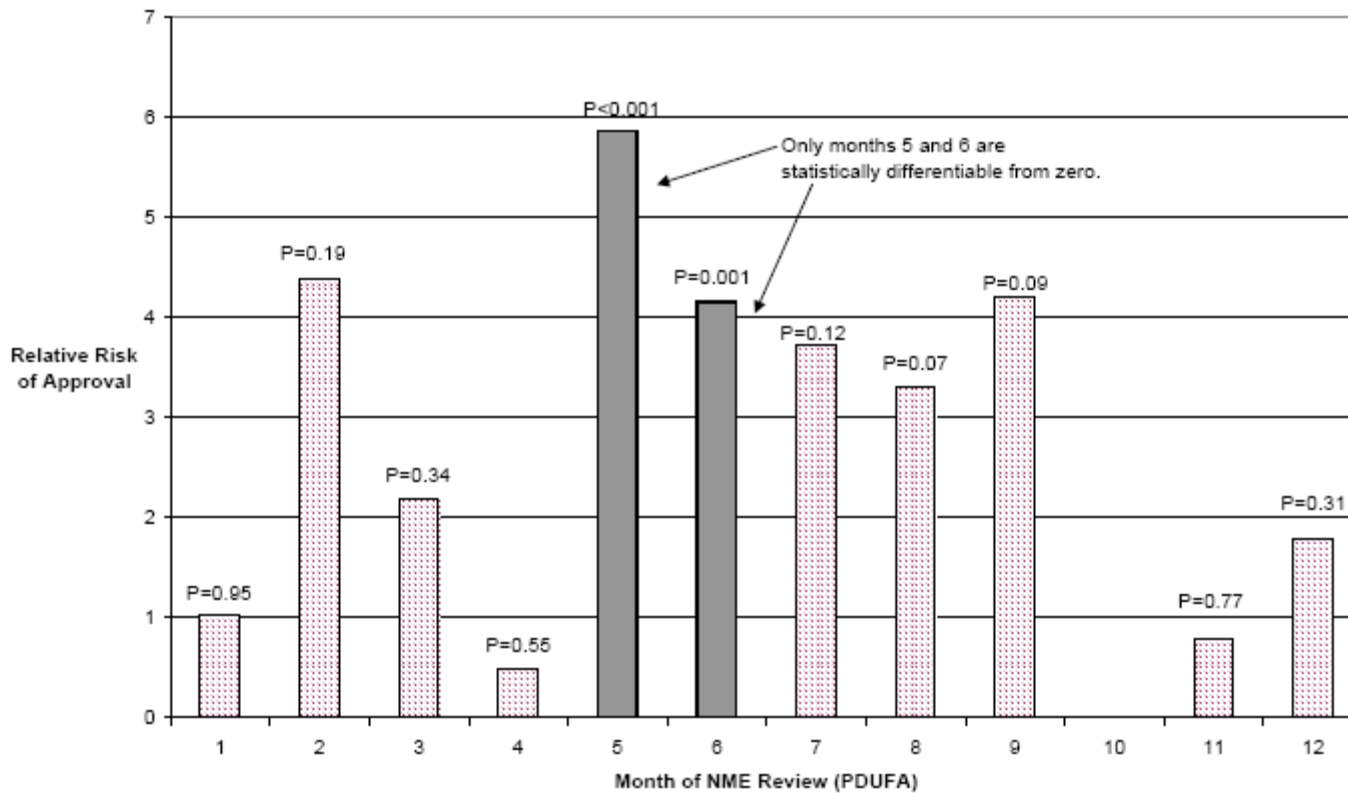
Appendix Figure 1:  
Approval Rate Ratios for the first 24 months of Drug Review  
for pre-PDUFA drugs, PDUFA I drugs and PDUFA II and later



**Results: The Two-Month Interval for Priority Drugs.**

Figure 2 shows that these patterns apply to priority drugs as well, where the deadline has been stable at six months over the 1993-2004 period.

**Appendix Figure 2: Relative Risk of Approval for Priority Drugs under PDUFA  
[PDUFA deadline for priority drugs is six months since 1992]**



The Cox models include the staff of the FDA’s drug reviewing division (CDER) as a covariate. The results in Appendix Table 1 show that the month-to-month relative risks are basically unaffected by the removal of this covariate from the equation, particularly for the just-before-deadline months. Only one of the review months (the ninth month of the PDUFA I review pattern) changes by more than seven percent in either direction.

**Appendix Table 1:  
Percentage Change in Relative Risk Estimates  
when CDER Staff Variable is Excluded from Model**

Month of Review, Standard NMES [PDUFA I]	Percentage Change in Relative Risk	Month of Review, Standard NMES [PDUFA II]	Percentage Change in Relative Risk	Month of Review, Priority NMES	Percentage Change in Relative Risk
1 <sup>st</sup>	-5.93%	1 <sup>st</sup>	0.35%	1 <sup>st</sup>	2.30%
2 <sup>nd</sup>	-6.83%	2 <sup>nd</sup>	1.20%	2 <sup>nd</sup>	1.44%
3 <sup>rd</sup>	-2.62%	3 <sup>rd</sup>	0.88%	3 <sup>rd</sup>	2.44%
4 <sup>th</sup>	-2.36%	4 <sup>th</sup>	-0.03%	4 <sup>th</sup>	2.70%
5 <sup>th</sup>	-1.63%	5 <sup>th</sup>	1.32%	5 <sup>th</sup>	2.23%
6 <sup>th</sup>	-1.72%	6 <sup>th</sup>	0.79%	6 <sup>th</sup>	2.68%
7 <sup>th</sup>	-1.18%	7 <sup>th</sup>	1.04%	7 <sup>th</sup>	2.44%
8 <sup>th</sup>	-1.57%	8 <sup>th</sup>	0.78%	8 <sup>th</sup>	2.15%
9 <sup>th</sup>	-11.08%	9 <sup>th</sup>	2.18%	9 <sup>th</sup>	4.46%
10 <sup>th</sup>	-0.25%	10 <sup>th</sup>	-0.34%	10 <sup>th</sup>	NA
11 <sup>th</sup>	-2.77%	11 <sup>th</sup>	0.11%	11 <sup>th</sup>	1.12%
12 <sup>th</sup>	2.94%	12 <sup>th</sup>	-0.02%	12 <sup>th</sup>	1.03%
13 <sup>th</sup>	0.53%	13 <sup>th</sup>	-0.40%		
14 <sup>th</sup>	1.55%	14 <sup>th</sup>	-0.55%		

Note: Two months preceding PDUFA deadline are shaded in gray. “NA” means that too few drugs are approved in the relevant month to form an estimate.

## II. Just-Before Deadline Approvals and Post-marketing Safety-Related Events: Further Observational Analyses.

We now present additional analyses of the postmarket safety events and the just-before-deadline measure.

In Appendix Table 2, we report basic results for logistic regression models with random effects. For each postmarket safety variable, we report two models in Table 2. The first excludes sponsor-specific indicators, while the second includes them.

The estimates in this table show essentially that the relationship between just-before-deadline approval status and postmarket safety problems is robust to the inclusion of random effects for primary indication of the drug and fixed effects for sponsor of the drug.

In Appendix Table 3, we present odds ratio estimates for the just-before-deadline variable for two models. Model 3A regresses the postmarket safety event of interest on the deadline indicator, an indicator variable scored “1” if the drug was approved in December (to control for the well-known December approval effect that arose in the late 1970s), and a variable measuring whether the drug was a priority or a standard NME. The results (appearing in the first row of estimates) show that the just-before-deadline effect is basically invariant to the inclusion of these variables. Model 3B puts in two covariates related to the primary indication of the drug – the annual number of hospitalizations associated with the indication disease, and the average length of those hospitalizations (in days). These results appear in the second row of estimates, and they show that the just-before-deadline effect is basically invariant to the inclusion of these variables.

In Appendix Table 4, we assess whether the just-before-deadline effect statistically interacts with two variables that change over the course of our dataset. The first is simply the submission year, which can be thought of as a linear time trend. The second is the total staff of the FDA’s drug reviewing division (CDER). The cell entries are odds ratio estimates for the interaction variable in question (this is specified in the leftmost column). The results from the table show that (1) there are no statistically significant interactions between the deadline effect and the passage of time since the enactment of PDUFA, and (2) there are no statistically significant interactions between the deadline effect and the number of staff in the FDA’s drug reviewing division. Thus the just-before-deadline effect appears to be somewhat “stable” over the twelve-year period covered by the data.

In Appendix Table 5, we present tests for the comparability of the drugs that were just-before-deadline approvals and just-after-deadline approvals. We do by limiting the sample to drugs that were either approved just before the deadline (the two months before the deadline) or that were approved just after the deadline (the two months following the elapsing of the deadline), and no other drugs. We then use linear regression (and in the case of the binary variable for advisory committee referral, logistic regression) to see whether selected covariates vary systematically from just-before-deadline to just-after-deadline

approvals. The results of Appendix Table 5 suggest that compared to just-after-deadline drugs, just-before-deadline drugs are no different in their order of entry to a therapeutic class, do not treat conditions with different hospitalization characteristics, do not treat conditions with different lethality, do not treat conditions with different incidence, and are not more likely to be referred to advisory committee.

[Appendix Tables 2 through 5 follow.]

**Appendix Table 2**  
**Mixed Effects Logistic Regression with Random Effects Terms for Primary Indication of NME**

[Approved Standard and non-Priority NMEs submitted January 1993 and afterwards]

Year of NME Submission	Global Safety-Based Withdrawal		Black-Box Warning		Withdrawal or Black-Box Warning		At Least One Dosage-Form Discontinuation	
	Random Effects Only	Sponsor Fixed Effects Added	Random Effects Only	Sponsor Fixed Effects Added	Random Effects Only	Sponsor Fixed Effects Added	Random Effects Only	Sponsor Fixed Effects Added
Odds Ratio in Bold, followed by p-value and 95% confidence interval	<b>0.80</b> (P = 0.09) 95% C.I. [0.63, 1.03]	<b>0.69</b> (P = 0.168) 95% C.I. [0.40, 1.16]	<b>1.26</b> (P = 0.03) 95% C.I. [1.02, 1.56]	<b>1.45</b> (P = 0.02) 95% C.I. [1.05, 2.01]	<b>1.09</b> (P = 0.29) 95% C.I. [0.93, 1.27]	<b>1.23</b> (P = 0.07) 95% C.I. [0.99, 1.53]	<b>0.82</b> (P = 0.01) 95% C.I. [0.71, 0.96]	<b>0.81</b> (P = 0.02) 95% C.I. [0.68, 0.97]
Just-Before-Deadline Approval  Odds Ratio in Bold, followed by p-value and 95% confidence interval	<b>5.71</b> (P = 0.01) 95% C.I. [1.52, 21.36]	<b>7.03</b> (P = 0.04) 95% C.I. [1.11, 44.60]	<b>4.79</b> (P = 0.02) 95% C.I. [1.26, 18.19]	<b>6.59</b> (P = 0.03) 95% C.I. [1.27, 34.13]	<b>4.55</b> (P = 0.003) 95% C.I. [1.69, 12.25]	<b>5.38</b> (P = 0.005) 95% C.I. [1.66, 17.39]	<b>3.65</b> (P = 0.002) 95% C.I. [1.62, 8.23]	<b>4.63</b> (P = 0.001) 95% C.I. [1.80, 11.86]
Number of Sponsor Effects Estimated	0	46	0	46	0	46	0	46
NMEs in estimation sample	313		313		313		295	

Notes: Dosage-form discontinuation sample smaller because NDA number match is not possible for all discontinuation records in FDA database; if no match is assumed to reflect no discontinuation, results are substantively identical. Sponsor Fixed Effects added only for sponsors (usually firms) with more than one NME submission in the period under study.

**Appendix Table 3**  
**Mixed Effects Logistic Regression with Random Effects Terms for Primary Indication of NME**

[Approved Standard and non-Priority NMEs submitted January 1993 and afterwards]

	Global Safety-Based Withdrawal	Black-Box Warning	Withdrawal or Black-Box Warning	At Least One Dosage- Form Discontinuation
<b>Model 3A:</b> Odds Ratio for Just-Before-Deadline Approval	<b>7.31</b>	<b>5.14</b>	<b>5.50</b>	<b>4.60</b>
Controlling for priority/standard status of NME and indicator for December approval	(P = 0.003)	(P = 0.03)	(P = 0.001)	(P = 0.001)
Odds Ratio in Bold, followed by p-value and 95% confidence interval	95% C.I. [1.93, 27.69]	95% C.I. [1.22, 21.68]	95% C.I. [1.93, 15.62]	95% C.I. [1.93, 10.97]
NMEs in estimation sample	313	313	313	295
<b>Model 3B:</b> Odds Ratio for Just-Before-Deadline Approval	<b>5.61</b>	<b>5.01</b>	<b>4.52</b>	<b>3.71</b>
Controlling total annual hospitalizations of drug's primary indication, and for average length of hospitalization (per hospitalization)	(P = 0.03)	(P = 0.02)	(P = 0.007)	(P = 0.006)
Odds Ratio in Bold, followed by p-value and 95% confidence interval	95% C.I. [1.19, 26.39]	95% C.I. [1.35, 18.58]	95% C.I. [1.50, 13.60]	95% C.I. [1.46, 9.43]
NMEs in estimation sample	265	265	265	252

Notes: Dosage-form discontinuation sample smaller because NDA number match is not possible for all discontinuation records in FDA database; if no match is assumed to reflect no discontinuation, results are substantively identical. None of the estimates for priority status or December approvals are statistically significant. Data not available on hospitalizations for all NME primary indications, hence Model 3B sample sizes are smaller.

<b>Appendix Table 4</b>				
<b>Tests for Interaction of Just-Before Deadline Approval with Year of Submission and CDER Staff Level</b>				
[Approved Standard and non-Priority NMEs submitted January 1993 and afterwards]				
	Global Safety-Based Withdrawal	Black-Box Warning	Withdrawal or Black-Box Warning	At Least One Dosage- Form Discontinuation
<b>Model 4A:</b> Odds Ratio for Just-Before-Deadline Approval Interacted with Year of Submission	<b>0.93</b>	<b>1.18</b>	<b>1.13</b>	<b>1.14</b>
	(P = 0.77)	(P = 0.45)	(P = 0.46)	(P = 0.40)
Odds Ratio in Bold, followed by p-value and 95% confidence interval	95% C.I. [0.56, 1.53]	95% C.I. [0.77, 1.82]	95% C.I. [0.82, 1.56]	95% C.I. [0.84, 1.55]
NMEs in estimation sample	313	313	313	295
<b>Model 4B:</b> Odds Ratio for Just-Before-Deadline Approval Interacted with CDER Staff (in thousands)	<b>0.003</b>	<b>0.81</b>	<b>1.75</b>	<b>6.21</b>
	(P = 0.36)	(P = 0.94)	(P = 0.81)	(P = 0.50)
Odds Ratio in Bold, followed by p-value and 95% confidence interval	95% C.I. [0.00, 661.71]	95% C.I. [0.002, 219.86]	95% C.I. [0.2, 169.28]	95% C.I. [0.00, 7972.81]
NMEs in estimation sample	313	313	313	295
Notes: Dosage-form discontinuation sample smaller because NDA number match is not possible for all discontinuation records in FDA database; if no match is assumed to reflect no discontinuation, results are substantively identical. Estimates for Model 4B are not stable; the just-before-deadline approval and interaction term with staff are highly correlated.				

**Appendix Table 5**  
**Tests Comparing NME Samples: Just-Before-Deadline vs. Just-After-Deadline Approvals**

Covariate	Association of Just-Before-Deadline Status with Covariate
Order of Entry in Therapeutic Class	OLS Coefficient: -5.68 P = 0.42 95% Confidence Interval: [-19.56, 8.20]
Total Hospitalizations of Primary Indication	OLS Coefficient: -5047.5 P = 0.85 95% Confidence Interval: [-55864.1, 45769.2]
Average Length of Hospitalization of Primary Indication (in days)	OLS Coefficient: -0.12 P = 0.90 95% Confidence Interval: [-1.92, 1.69]
Age-Adjusted Death Rate of Primary Indication (per 100,000)	OLS Coefficient: 0.0081 P = 0.66 95% Confidence Interval: [-0.04, 0.03]
Incidence of Primary Indication (per 100,000)	OLS Coefficient: -102.87 P = 0.20 95% Confidence Interval: [-261.27, 55.52]
Probability of Advisory Committee Referral (binary)	Relative Risk (Logistic Regression): 1.29 P = 0.50 95% Confidence Interval: [0.62, 2.72]
Note: Each entry is the coefficient in a regression of the just-before-deadline indicator with the covariate in the left column. The sample is restricted to NMEs (N = 149) that are approved within the two months before PDUFA deadline (just-before-deadline) and NMEs approved within the two months after the deadline (“just-after-deadline”).	

III. Analyses using the Approval Time of the NME itself as a Regressor.

<p style="text-align: center;"><b>Appendix Table 6</b>  <b>Tests for Association between NME Approval Time and Postmarket Safety Problems</b>                      [Approved Standard and non-Priority NMEs submitted January 1993 and afterwards]</p>				
	Global Safety-Based Withdrawal	Black-Box Warning	Withdrawal or Black-Box Warning	At Least One Dosage- Form Discontinuation
Odds Ratio for NME Approval Time (in months) [controlling for year of submission and random effects for NME primary indication, as in Appendix Table 2]  Odds Ratio in Bold, followed by P-value and 95% confidence interval	<b>0.96</b>  (P = 0.30)  95% C.I. [0.90, 1.03]	<b>0.97</b>  (P = 0.35)  95% C.I. [0.90, 1.03]	<b>0.96</b>  (P = 0.19)  95% C.I. [0.91, 1.02]	<b>0.98</b>  (P = 0.44)  95% C.I. [0.95, 1.02]
NMEs in estimation sample	313	313	313	295

#### IV. Analyses of Postmarket Safety Problems Using Alternative Windows for Just-Before-Deadline Status.

One might wonder whether the results of the paper hold up if the definition of a “just-before-deadline” approval is changed. Table 7 presents mixed-effects logistic regressions under three measures of just-before-deadline approval. In Model 7A a just-before-deadline approval is defined as approval in the last month before the deadline elapses (for standard NMEs under PDUFA 1, these are twelfth-month approvals, for standard NMEs under FDAMA and afterwards, these are tenth-month approvals, while for priority drugs under all of the user-fee acts, these are sixth-month approvals). In Model 7B the two-month window used in the paper is employed, which repeats the mixed-effects model results presented in Appendix Table 2. In Model 7C a three-month window is employed. Notice that all the odds ratio estimates are above one and are statistically significant, but that there is a sizable drop in estimate size, in statistical significance, and in model log likelihood when the three month window is employed. The models with one-month and two-month windows display very similar estimates and properties.

<b>Appendix Table 7</b>				
<b>Tests for Interaction of Just-Before Deadline Approval with Year of Submission and CDER Staff Level</b>				
[Approved Standard and non-Priority NMEs submitted January 1993 and afterwards]				
	Global Safety-Based Withdrawal	Black-Box Warning	Withdrawal or Black-Box Warning	At Least One Dosage- Form Discontinuation
<b>Model 7A:</b> Odds Ratio for Just-Before-Deadline Approval defined as Approval in the 1 month before PDUFA deadline	<b>5.10</b>  (P = 0.01) 95% C.I. [1.41, 18.37]  Log-Likelihood = -43.64	<b>5.35</b>  (P = 0.01) 95% C.I. [1.49, 19.18]  Log-Likelihood = -47.69	<b>4.88</b>  (P = 0.001) 95% C.I. [1.87, 12.71]  Log-Likelihood = -69.59	<b>3.36</b>  (P = 0.003) 95% C.I. [1.52, 7.43]  Log-Likelihood = -102.38
<b>Model 7B:</b> Odds Ratio for Just-Before-Deadline Approval defined as Approval in the 2 months before PDUFA deadline	<b>5.71</b>  (P = 0.01) 95% C.I. [1.53, 21.36]  Log-Likelihood = -43.36	<b>4.78</b>  (P = 0.02) 95% C.I. [1.26, 18.19]  Log-Likelihood = -48.21	<b>4.55</b>  (P = 0.003) 95% C.I. [1.69, 12.25]  Log-Likelihood = -70.28	<b>3.64</b>  (P = 0.002) 95% C.I. [1.62, 8.23]  Log-Likelihood = -101.95
<b>Model 7C:</b> Odds Ratio for Just-Before-Deadline Approval defined as Approval in the 3 months before PDUFA deadline	<b>3.75</b>  (P = 0.04) 95% C.I. [1.04, 13.43]  Log-Likelihood = -44.74	<b>3.74</b>  (P = 0.04) 95% C.I. [1.04, 13.44]  Log-Likelihood = -49.08	<b>3.50</b>  (P = 0.01) 95% C.I. [1.33, 9.22]  Log-Likelihood = -71.71	<b>2.31</b>  (P = 0.03) 95% C.I. [1.07, 4.98]  Log-Likelihood = -104.74
NMEs in estimation sample	313	313	313	295
Notes: Odds Ratio in Bold, followed by p-value and 95% confidence interval. Dosage-form discontinuation sample smaller because NDA number match is not possible for all discontinuation records in FDA database; if no match is assumed to reflect no discontinuation, results are substantively identical.				