

The December Effect in FDA Drug Approvals: Assessing the Submissions Echo Hypothesis

James B. Graham, MBA, SM
McKinsey & Company,
Boston, Massachusetts

Ernst R. Berndt, PhD
Massachusetts Institute of
Technology, Cambridge,
Massachusetts; and
National Bureau of
Economic Research

[Q1]

It has been documented that the Food and Drug Administration's new drug approvals occur disproportionately in the month of December. We hypothesize that the observed excess December approvals reflects an excess of December New Drug Application (NDA) and Biologics License Application (BLA) submissions. Furthermore, we expect this pattern to have become more pronounced following the passage of the Prescription Drug User Fee Act (PDUFA) in 1992, which set explicit 6- and 12-month review targets. We call this the "December submissions echo" hypothesis. Contrary to our hypothesis, we find the excess December approval phenomenon to be even more pronounced before PDUFA than following it.

Although the monthly pattern for NDA/BLA approvals varied minimally upon enactment of PDUFA, the proportion of NDA/BLA December submissions increased considerably in the post-PDUFA period and has continued to increase recently. As expected, PDUFA review time targets of 6 and 12 months lead to spikes in approvals around these time periods. Although the December excess approval phenomenon has been mitigated recently in response to 10-month-review targets in PDUFA II, the excess December submission phenomenon has persisted since 2001. We consider implications for FDA workloads, first-cycle approvals, industry submission strategies, and user fee policies.

Key Words

Prescription Drug User Fee Act (PDUFA);
Food and Drug Administration (FDA);
Seasonality

[Q2]

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INTRODUCTION

Food and Drug Administration (FDA) new drug approvals occur disproportionately in the month of December. The Tufts Center for the Study of Drug Development has reported that, of the 107 New Chemical Entity approvals from 1995 to 1997, 29 (27%) occurred in the month of December (1). Seasonal variations are also apparent in New Drug Application (NDA) submissions. A recent study commissioned by the FDA found that from fiscal years 2001 through 2004, fourth-quarter NDA submissions outnumbered submissions in other quarters by a factor of two to three (2).

The Prescription Drug User Fee Act of 1992 (PDUFA I) set review targets of 6 months for priority applications and 12 months for standard applications (3). On the basis of these targets, FDA approval decisions delivered in accordance with PDUFA guidelines would be expected to lag NDA and Biologics License Application (BLA) submission dates by 6 or 12

months, assuming that reviews are completed near their respective deadlines. Elevated NDA/BLA submissions in one or more months could lead to subsequent "echo effect" increases in approvals 6 and 12 months later based on PDUFA I review period targets.

Here we report results of an analysis investigating the linkage between seasonality in NDA/BLA submissions and approvals. Specifically, we hypothesize that elevated December submissions result in the observed elevation in December approvals. We label this the "December submissions echo" hypothesis. Further, we hypothesize that PDUFA I strengthened the link between seasonal variations in submissions and approvals by specifying review time lines. We also hypothesize that 1997 and 2002 PDUFA renewals (PDUFA II and PDUFA III, respectively), which reduced the target standard review time from 12 months to 10 months, have shifted the seasonal elevation of NDA approvals to October and November, reducing the proportion of December approvals.

METHODS

We define the set of “New Therapeutic Entities” (NTEs) to be New Molecular Entities and therapeutic biological products. Initial data on NTE submissions and approvals were provided by FDA.¹ As described previously in Berndt, Gottschalk, and Strobeck (2005) (4), the data set analyzed contains all NMEs and therapeutic BLAs approved from 1965 through 2003, inclusive. Data recorded includes generic name, developing company and country, FDA approval date, IND submission date, PDUFA date for receipt of complete application, IND number, elapsed approval time (months), years from IND submission to NDA submission, total development years (IND submission through NDA approval), NDA/BLA number, and US marketing date (year and month). We have updated this data set through 2005 using published FDA reports and press releases. Statistical analysis of submission and approval frequency distributions were tested for nonuniformity using the χ^2 method described in Bertsimas and Freund (2000) (5). Data analyses were performed using Microsoft Excel 2003 with the Analysis ToolPak module.

RESULTS

Figure 1 documents the December effect for four time periods: the pre-PDUFA I period (1965–1992), the PDUFA I period (1992–1997), the post-PDUFA I period (1997–2005), and the entire analyzed period (1965–2005). For the 997 NTEs approved between 1965 and 2005, 226 (23%) were approved in December.

The null hypothesis that approvals occur uniformly among the 12 months is decisively rejected for the overall period and for each of the subperiods. A χ^2 test for uniform distribution confirms that for each of these time periods, the monthly distribution of approvals deviates significantly from uniformity ($P < .001$). If December is excluded, uniformity cannot be rejected for the remaining 11 months.

After implementation of PDUFA I targets in 1992, the percentage of NDAs and BLAs reviewed within PDUFA guidelines increased from 55% in 1994 to 90% in 1997 (3). The im-

pact of PDUFA on review times is evident in histograms comparing approval times for NDAs and BLAs submitted before and after PDUFA I became effective in September 1992. Figure 2 shows the distribution of review times for the 541 NTE applications approved from 1965 up to the implementation of PDUFA I in 1992. Approval periods ranging between 12 and 24 months are slightly more common, but no period dominates. Approximately 15% of NTE approval periods exceeded 48 months.

By contrast, as we show in Figure 3, in the PDUFA I period (dating from the PDUFA I effective date of September 1, 1992, through its expiration on September 30, 1997), review periods of 6 and 12 months became more common. Seventeen percent of NTE applications submitted in the PDUFA I period were approved in 12 months, and 6% were approved in 6 months.

Figure 4 documents the volume of NTE applications submitted (not approvals) by month for the same time periods included in Figure 1. Over the PDUFA I time period, 33 NTE applications were submitted in December, 50% more than the 22 NTEs submitted in June, the second most frequent month. Although June submissions are outliers, they are much closer to the overall monthly average of 16 than are those for December. Also notable from Figure 4 are the elevations in submission volumes that occur in March, June, September, and December, the last month of each fiscal quarter for firms with conventional fiscal year ends.

Compared with the years before PDUFA I, December submissions increased substantially in the PDUFA I period. Before PDUFA I, NTE application submissions were relatively evenly distributed across all months. The most frequent month for submissions was March, followed by December. For the PDUFA I period between 1992 and 1997, 18% of NTE applications were submitted in December, double the overall average. This trend has continued and strengthened during the PDUFA II and III periods, with 26% of NTE submissions occurring in the month of December since 1997.

For the PDUFA I period, the elevation in the

[Q3]

NTE approvals by calendar month, 1965–2005.								
Month	Pre PDUFA I		PDUFA I		Post PDUFA I		Overall	
	Approvals	Percent	Approvals	Percent	Approvals	Percent	Approvals	Percent
January	28	5.2%	5	2.6%	10	3.7%	43	4.3%
February	32	5.9%	9	4.8%	16	6.0%	57	5.7%
March	33	6.1%	13	6.9%	22	8.2%	68	6.8%
April	33	6.1%	11	5.8%	22	8.2%	66	6.6%
May	39	7.2%	14	7.4%	25	9.4%	78	7.8%
June	47	8.7%	17	9.0%	18	6.7%	82	8.2%
July	41	7.6%	11	5.8%	21	7.9%	73	7.3%
August	34	6.3%	9	4.8%	22	8.2%	65	6.5%
September	35	6.5%	28	14.8%	16	6.0%	79	7.9%
October	48	8.9%	9	4.8%	20	7.5%	77	7.7%
November	42	7.8%	10	5.3%	31	11.6%	83	8.3%
December	129	23.8%	53	28.0%	44	16.5%	226	22.7%
	541	100.0%	189	100.0%	267	100.0%	997	100.0%

FIGURE 1

number of NTE submissions in December is statistically significant. The expected magnitude of the December submissions' echo effect can be estimated conservatively by multiplying the number of excess December submissions ($17.3 = 33.0 - 16.7$) by the percentage of submitted applications approved in exactly 12

months (17%), which results in an estimated excess of 2.9 NTE approvals in December compared with the average over other months.

It is illuminating to compare this estimated 2.9 excess December NTE approvals with actual historical data. Actual monthly NTE approval data in the PDUFA I period are present-

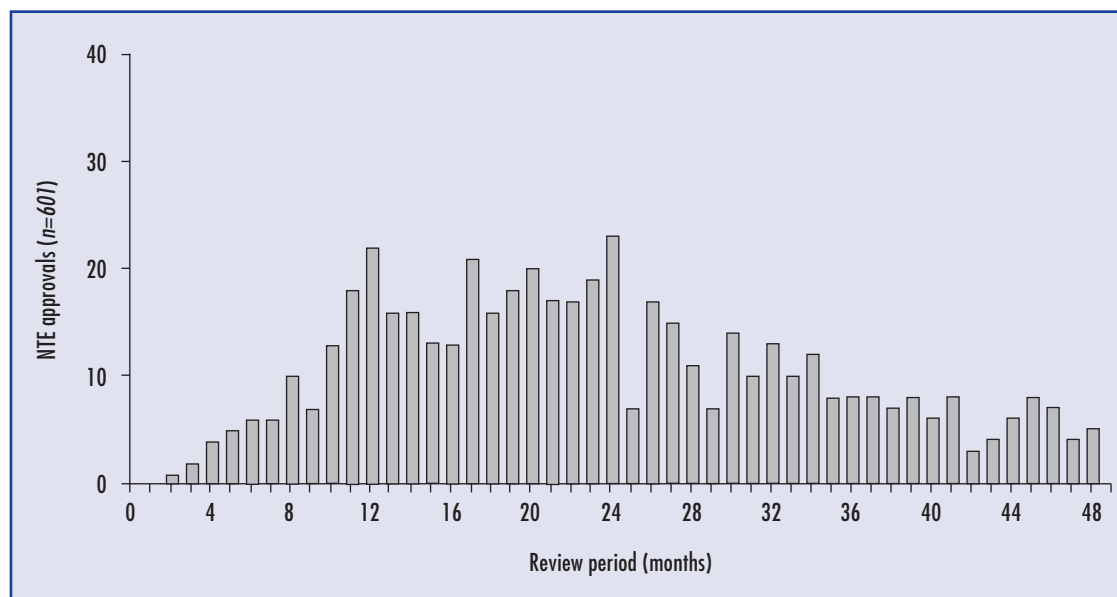
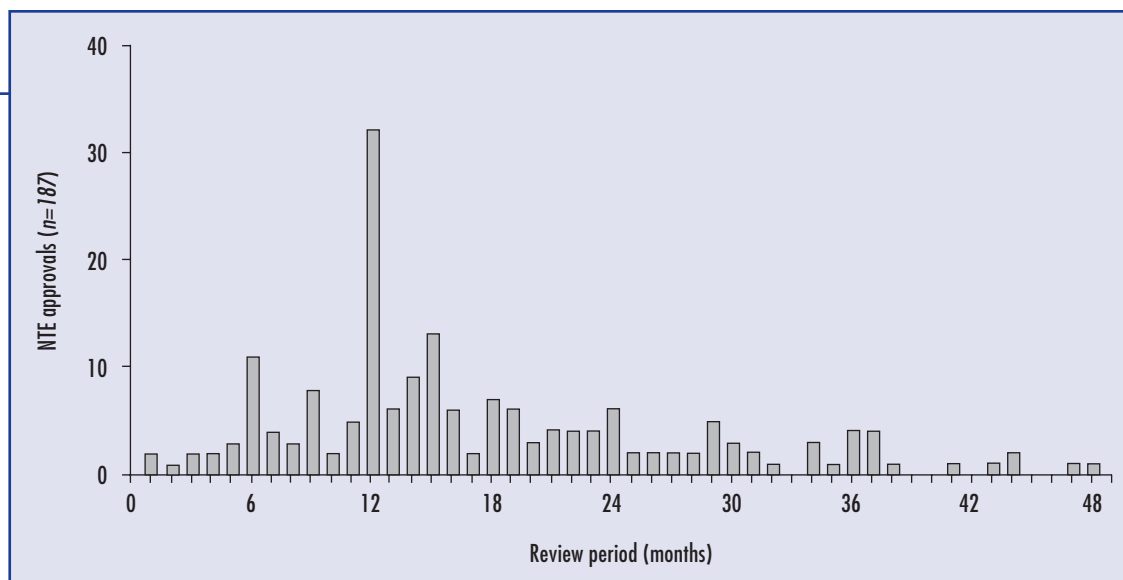


FIGURE 2

Review times for NTEs approved before PDUFA I (January 1, 1965, through August 31, 1992).

FIGURE 3

Review times for NTEs approved during PDUFA I (September 1, 1992, through September 30, 1997).



ed in Figure 1. As we noted earlier, the mean number of approvals per month is 15.8. Adding the conservative estimate of 2.9 additional approvals from the simple submissions echo hypothesis yields an estimated December approval volume of approximately 18.7 NTEs. In actuality, however, December ap-

proval volume in excess of the average is 37.2 NTEs (53.0 – 15.8), over 12 times more than the estimated 2.9 increased expected based on the simple submissions echo hypothesis alone.

A more aggressive estimate of the impact of the December submissions effect proceeds as

FIGURE 4

NTE submissions by calendar month, 1965–2005.								
	Pre PDUFA I		PDUFA I		Post PDUFA I		Overall	
Month	Submissions	Percent	Submissions	Percent	Submissions	Percent	Submissions	Percent
January	40	6.6%	12	6.4%	13	6.3%	65	6.5%
February	55	9.1%	12	6.4%	10	4.8%	77	7.7%
March	75	12.5%	19	10.1%	15	7.2%	109	10.9%
April	56	9.3%	16	8.5%	13	6.3%	85	8.5%
May	46	7.6%	9	4.8%	9	4.3%	64	6.4%
June	43	7.1%	22	11.7%	22	10.6%	87	8.7%
July	48	8.0%	15	8.0%	12	5.8%	75	7.5%
August	39	6.5%	10	5.3%	12	5.8%	61	6.1%
September	42	7.0%	20	10.6%	17	8.2%	79	7.9%
October	42	7.0%	8	4.3%	19	9.2%	69	6.9%
November	47	7.8%	12	6.4%	11	5.3%	70	7.0%
December	69	11.5%	33	17.6%	54	26.1%	156	15.6%
	602	100.0%	188	100.0%	207	100.0%	997	100.0%

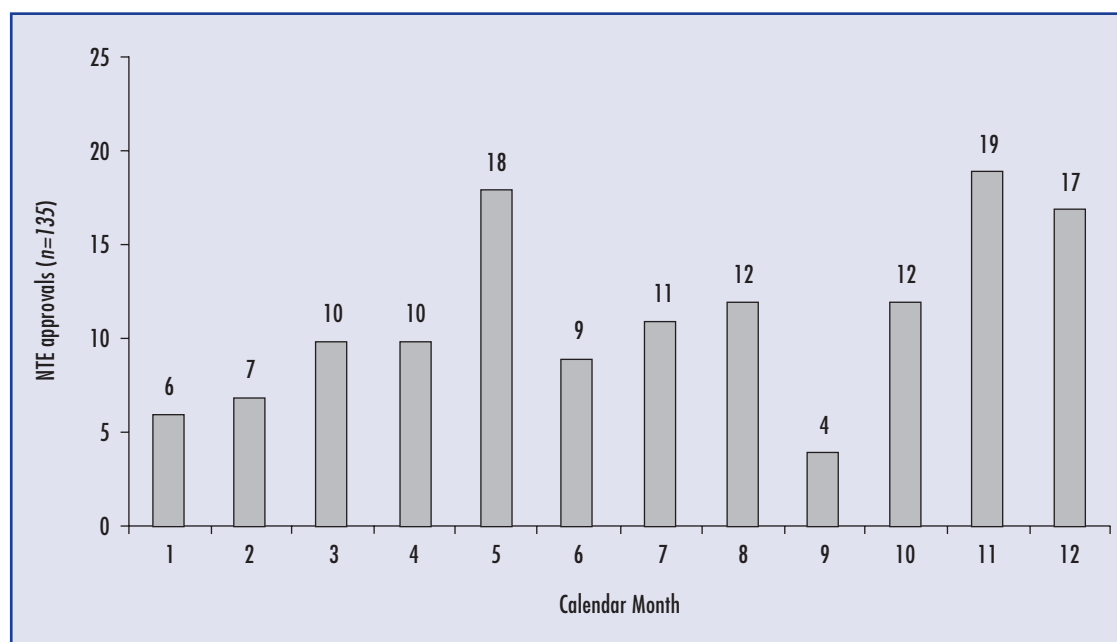


FIGURE 5

NTE approvals by calendar month, 2001–2005.

follows. If all (rather than 17%) excess December submissions (173) are assumed to be approved at PDUFA-mandated 12- and 6-month lags, and if the historical proportion of standard to priority applications (60:40) is assumed to hold, then an excess of 10 approvals would be predicted for December and 7 for June. Even in this aggressive case, however, the predicted excess does not account for the full magnitude of the December effect (37). In addition, the submissions echo hypothesis predicts a secondary peak in NTE approvals in June, when priority applications submitted in December are reviewed and acted on or approved. However, Figure 1 indicates that June NTE approvals are only slightly elevated compared with other months.

Finally, Figure 5 suggests that the dominance of December for NTE approvals may be waning recently. For the 135 applications approved since 2001, December is no longer the dominant approval month. Rather, May, November, and December now account for relatively more approvals compared with other months. The volume of NTE approvals since 2001 is more evenly distributed than in other periods analyzed previously, and the null hypothesis of uniform distribution cannot be rejected at the 95% confidence level.

DISCUSSION

We can summarize results from this analysis as follows: The evidence presented supports the submissions echo hypothesis that the combined effects of elevated December NTE application submissions and the established 12-month PDUFA review target resulted in a marginal increase in December NTE approvals. However, the magnitude of the observed December approvals effect greatly exceeds the expected increase based on the submissions echo hypothesis alone. In addition, the submissions echo hypothesis predicts an elevation in post-PDUFA NTE approvals in June. Observed approval patterns are not consistent with this prediction.

Further, if the submissions echo hypothesis were the primary cause for the December approvals effect, one would not expect to observe the December approval effect before the implementation of PDUFA I, since before PDUFA I, regulatory time lines did not specify the review period between submission and approval. The finding that the December approvals effect existed before the implementation of PDUFA weakens the hypothesis that this effect is primarily the result of industry submission practices coupled with PDUFA review guide-

lines. Although the combination of industry submission schedules and PDUFA review times partially explains the December approvals effect, it only accounts for a small portion of the observed increase. What accounts for the remaining gap?

It is unclear why the December effect existed before the implementation of PDUFA. One possibility is that FDA reviewers follow seasonal work patterns organized around the calendar year. Related to this, September, the last month of the US federal government fiscal year, was the second most frequent NTE approval month, with 15% of approvals. It is possible that FDA reviewers may face implicit incentives to act on applications around calendar year-end, to clear out pending submissions. FDA annual reports occasionally include workflow metrics, including the number of new drugs approved during a particular calendar year (6,7).² Investors and biopharmaceutical industry interest groups closely monitor the performance of the FDA and may focus on the agency's annual report as the basis for analysis and critique (see, for example, Refs. 8,9,10).

[Q4]

We also observed that while the implementation of PDUFA I had little effect on the monthly distribution of approvals, the proportion of December NTE submissions patterns increased steadily from 11.5% before PDUFA I, to 17.6% during the PDUFA I period, to 26.1% in the PDUFA II and PDUFA III periods. It is unclear why industry sponsors have increasingly favored December submissions. Industry management may prefer to announce NDA/BLA filings near the company fiscal year-end, which, in most cases, coincides with the calendar year end in December. Alternatively, the increasing number of December submissions could reflect FDA reviewer preferences. Through pre-filing discussions, FDA reviewers could potentially guide sponsors toward December submissions. However, according to John Jenkins, MD, Director of the FDA's Office of New Drugs at the Center for Drug Evaluation and Research, this is not the case. He recently stated: "We have no control on the incoming workload or the quality of the applications. We can't set goals for approvals

or approval times for a year; they depend on what we get and the quality of what we get" (9, p. A3). Additional inquiry is needed to isolate and interpret the causes for the observed December effect in submissions.

The FDA Modernization Act of 1997 included an update to PDUFA I guidelines. This update, known as PDUFA II, added provisions to reduce the review period target from 12 months to 10 months for standard NTE applications. Specific performance targets were structured as follows: 30% of standard applications reviewed within 10 months in FY1999, 50% in FY2000, 70% in FY2001, and 90% in FY2002 and thereafter. In 2003, the FDA reported that it had achieved the 10-month review target for standard NTE applications in 81% of cases in 2001 and 95% of cases in 2002 (3).

With the 10-month review target specified under PDUFA II, the December effect for submissions or approvals (or both) would be expected to change. Data collected from 2001 (when PDUFA's 10-month targets were 81% implemented) to 2005 indicate that the December effect in approvals is weakening, while the December effect in application submissions remains robust. This observation is corroborated by a recent FDA-commissioned report on first-cycle reviews that noted "the FDA receives between two and three times the number of submissions in the fourth quarter compared to any other quarter in the calendar year" (2). [Q5]

It is interesting that the report also disclosed that fourth-quarter applications have the lowest rate of first-cycle approval (2, p. v). Whereas 64% of submissions in the first three quarters of the year were approved in the first review cycle, only 25% of the fourth-quarter submissions received first-cycle approval (2, 11).³ Analyses of data indicated no difference in the quality of fourth-quarter applications compared with submissions in other quarters. The report suggested FDA staffing workload challenges as a potential reason for the relatively lower rate of first-cycle approvals for fourth-quarter submissions.

Recognizing the reduced rates of first-cycle approval for fourth-quarter submissions, sponsors may consider designing regulatory strate-

gies to avoid submission in this period. In addition, the FDA may consider altering user fee schedules and review targets to manage workload seasonality more effectively in the PDUFA renewal slated for 2007. For example, a user fee premium could be levied on fourth-quarter submissions, or target review times could be extended for these submissions to improve staffing and workload management. Alternatively, the FDA could agree to set up sponsor meetings more quickly in the first three quarters of the year. Care would need to be taken, however, to ensure that provisions would promote the intended submission behavior and would not result in unintended consequences such as gaming of submission dates, thereby reducing potential workload and staffing benefits from a smoother submission profile.

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NOTES

1. We gratefully acknowledge data support from Ed Hass of the US FDA Office of Policy and Planning, who has since retired.
2. This contrasts with the perception of a slowdown in US innovation activity in the 1970s as reflected in a decline in application approvals granted by the US Patent and Trademark Office. Belatedly, observers discovered that the patent-approval slowdown reflected a sharp decline in the number of patent examiners employed. See Griliches (6,7) for discussion.
3. Ref. 2, exhibit 32, p. 27. Additional FDA workload issues surrounding renewal of the Prescription Drug User Fee Acts are discussed in Ref. 11 and in Usdin (8,9,10).

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[Q6]

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[Q7]

