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Internal Deadlines, Drug Approvals, and Safety Problems[†]

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Absent explicit quotas, incentives, reporting, or fiscal year-end motives, drug approvals around the world surge in December, at month-ends, and before respective major national holidays. Drugs approved before these informal deadlines are associated with significantly more adverse effects, including more hospitalizations, life-threatening incidents, and deaths—particularly, drugs most rushed through the approval process. These patterns are consistent with a model in which regulators rush to meet internal production benchmarks associated with salient calendar periods: this "desk-clearing" behavior results in more lax review, leading both to increased output and increased safety issues at particular—and predictable—periodicities over the year. (*JEL* D83, I11, L51, L65)

In this paper we document a global surge in drug approvals preceding informal deadlines. These include spikes in the month of December, at the end of each calendar month, and just before important national holidays in respective countries. The magnitude of these effects is striking: for instance, across a dataset spanning drug approvals in the United States, the European Union, Japan, China, and South Korea, 18.64 percent of all approved drugs are approved in the month of December—more than double the average in any other month. Moreover, we examine the safety ramifications of these approval surges. Holding constant disease type, year, and various other controls, drugs approved just before informal deadlines are associated with significantly more adverse effects, including more hospitalizations, life-threatening incidents, and deaths.[1]

The approval patterns we observe exist at periodicities consistent with regulators rushing to meet internally imposed benchmarks associated with calendar events such as year-ends, month-ends, and holidays. In particular, while Carpenter, Zucker, and Avorn (2008) have shown that drug regulators rush to meet formal deadlines in the United States, we identify a distinct behavioral phenomenon that persists across

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[1] We observe adverse effects data for the United States and European Union; disaggregated data on serious adverse effects are available from the US sample only.

different formal regulatory regimes in many countries. For example, drug regulators are not formally evaluated on their year-end output in any country that we are aware of; rather, they are typically given target times for processing applicants and evaluated in part based on the percentage of applications that receive a timely review. These specific targets differ across regulators in different countries (within 300 days in the United States versus 210 days in the European Union, for instance). Rushing to comply with these formal policies would not generate the pattern of year-end, month-end, and holiday surges that we document.

We argue, instead, that these patterns are more consistent with an interpretation in which regulators use salient calendar-time periods to clear their workloads so that they can start with a "clean" desk in the next period. Consistent with this interpretation, we show that regulators approve an especially large number of drugs in December in years when they have approved relatively few drugs in the first part of the year. Moreover, December drugs approved during these especially busy months are associated with even more adverse effects. This suggests either that regulators engage in hastier desk clearing when their workload is high (e.g., when there are more drug candidates left to be decided upon in December) or when they feel greater informal pressure to increase output (e.g., when their approval numbers look low leading into December).[2]

We provide evidence that our findings are not driven by a number of alternative explanations. First, it is possible that regulatory bodies may evaluate different types of drugs in December or at the end of each month. Regulators may, for instance, collect their most complex cases throughout the year or month to be considered at the end of that period. In this case, the higher adverse effects that we see for drugs approved during these periods would reflect the nature of the drugs themselves rather than the quality of the decision-making process that led to their approval. To explore this possibility, we examine whether there are ex ante differences among drugs approved during output surges that may explain their ex post differences in adverse effects. We show that controlling for a battery of drug characteristics—the disease meant to be treated, market size, and the drug's priority review status—does not alter our findings, suggesting that our results are not driven by differences on these dimensions. We further show that drugs approved in December do not appear to be more complicated or difficult to review as explicitly measured by their chemical or functional novelty.

It is also possible that firms time application submissions in the hopes of receiving a lax December review. Using information on application dates available for a subset of US drugs, we find no evidence that the December effect is generated by strategic timing, which would generate a surge of applications in February (for regular review) or June (for priority review).

If regulators make rushed decisions to meet internal deadlines, a natural question is why they seem to err on the side of approval rather than rejection. We believe this may be the result of informal performance benchmarks that focus on the quantity of drugs that are approved rather than the quality of those decisions. The number of drugs that are approved is immediately visible and likely to be much more salient than an approved drug's adverse effects, which may take years to be realized.

[2] Distinguishing between these possibilities requires knowing the date on which rejected drug candidates are rejected. Unfortunately this is unobserved.

Indeed, in the public discourse, drug regulators across the world are evaluated and compared on the basis of their drug output. This, combined with the fact that industry and patient groups typically advocate for the approval rather than rejection of new drugs, may bias regulators toward approval.

Finally we consider the policy implications of our findings. First, we note that the welfare implications of our findings are unclear. One possibility, of course, is that a rushed review process decreases public welfare by increasing the likelihood that dangerous drugs enter the market. However, if regulators were generally too conservative in new drug approvals, then rushed review may actually be welfare improving—even given an increase in adverse effects—because it moves the review standard closer to first best. Because we cannot observe the benefits that accrue to patients administered these drugs, our analysis cannot distinguish between these two possibilities. That said, we do perform a back-of-the-envelope estimation to get a sense of the magnitude at least of the costs associated with this pattern of rushed review. Our calculation suggests that between 1,400 and 9,000 lives are lost per year to rushed review; given a low-end estimate of the value of a statistical life ($885,000 per life), this works out to roughly $1.2 to $8 billion implied loss per year over our sample period.

That said, even if a drug approval agency were broadly too conservative in its approval decisions across all drugs, an optimal policy response would not be to apply more lax screening *only* to those drugs nearing approval at the end of the year or month.[3] We outline two potential policy responses, one based on a mandated smoothing of approvals over time and another based on using a "holding-tank" mechanism in which some drugs approved during high-volume periods are slated for re-review prior to receiving a final go-ahead.

Situating our work in the literature, production targets—both formal and informal—are ubiquitous across the economy, and similar spikes in output have been documented in settings ranging from sales (Larkin 2014, Oyer 1998) to patent office approvals (Blatt and Huang 2018), judicial decisions (Gelbach and Marcus 2017), and spending at federal agencies (Liebman and Mahoney 2017).

Moreover, trading off costs and benefits in intertemporal choice, and models surrounding seeming behavioral irregularities in this decision-making, go back to Strotz (1955) and Phelps and Pollak (1968), continuing through the hyperbolic discounting models of Laibson (1997) and O'Donoghue and Rabin (1999a, 1999b). The experimental and empirical literature has further established a strong behavioral tendency of procrastination, to which "deadlines" have been proposed as solutions. More specifically, O'Donoghue and Rabin (1999b) show how incentive schemes with "deadlines" may be a useful screening device to distinguish efficient delay from inefficient procrastination.

Our work is most closely related to Carpenter, Zucker, and Avorn (2008) and Carpenter et al. (2012), both of which study the impact of formal deadlines imposed by the US Prescription Drug User Fee Act of 1992 on drug approvals; they find that more drugs are approved prior to their review deadlines and that drugs approved-

[3] As we see no spikes in "days under consideration" for drugs in December, it is not that agencies are saving their most difficult cases for year- or month-end (or before holidays). Nor do we see any strategic timing in terms of submissions on the side of drugmakers in terms of their submission timing of drugs.

during these periods are more likely to face post-marketing safety problems.[4] In addition, Carpenter (2014) documents an elevated share of drug approvals occurring in December but does not explore the causes or safety consequences of this.

Our work makes three key contributions relative to this body of existing literature. First, we show that regulators across the globe appear to strongly respond to common informal deadlines based on psychological benchmarks that are independent of externally imposed administrative deadlines. Second, we find that drugs approved during these output surges have substantially more adverse health effects relative to drugs approved at other times. These results provide evidence that informal deadlines can distort drug approvals just as much as formal deadlines.[5]

Finally, we show that—precisely because they are not generated by any specific administrative policy—these behavioral responses to informal deadlines are a robust worldwide phenomenon. Such patterns highlight the importance of developing policy responses to address non-policy-induced inefficiencies in behavior.

I. Background on Drug Approvals

Drugs cannot be widely marketed without regulatory approval from country- or region-level agencies. The decisions of these agencies determine what treatments are available to patients and who profits as a result.

Seeking agency approval is the final step in a drug development process that is lengthy, expensive, and uncertain. Firms typically test thousands of compounds to find one with enough therapeutic potential to be tested in humans. Human clinical trials, further, involve thousands of patients and typically last for five to ten years. On average, 90 percent of drug candidates that enter human trials do not make it through approval (DiMasi, Hansen, and Grabowski 2003).

Drug approval decisions can impact the safety of drugs in two main ways. First, drugs vary in their inherent risks, and regulators select which drugs to approve. If regulators approve more inherently dangerous drugs, this would increase the safety issues we see in the data. Second, the regulator does not make a simple approve-or-not binary decision. Rather, regulators look through clinical trial data and approve drugs in specific doses for specific indications with specific contraindications. If regulators rush their review, they may approve a drug at an unsafe dosage or fail to highlight a potentially dangerous drug interaction.

The specifics of drug approval processes vary across agencies but generally follow the same overall process. A firm submits a drug approval application to the regulatory agency responsible for their targeted market. The application typically describes the drug's intended use (labeling); includes a detailed description of the drug's chemical formulation, pharmacodynamics (how it affects the body), and pharmacokinetics

[4] See also Nardinelli, Lanthier, and Temple (2008) and Schick et al. (2017), however, for evidence that challenges the robustness of these original findings. More generally, also see Darrow, Avorn, and Kesselheim (2017) for a review of the interplay between incentives, user fees, and the timeliness and safety of FDA approvals and Darrow and Kesselheim (2014) for a list of important legislative and regulatory events related to the FDA's new drug approval process, along with Kesselheim et al. (2015) for recent trends in expedited approval program use.

[5] See Carpenter and Grimmer (2009) and Balasubramanian, Lee, and Sivadasan (2018) for theories of how formal deadlines and deadline-related time pressures can impact work quality. Also see Brunnermeier, Papakonstantinou, and Parker (2008) and Buehler, Griffin, and Ross (1994) for theory and evidence on the planning fallacy and the imposition of self-imposed deadlines.

(how the body affects it); provides a compilation of all results from prior pre-clinical and clinical trials; and describes the drug manufacturing methods that will be used. The application's length can reach upward of 100,000 pages of material (Van Norman 2016). In the United States, the Food and Drug Administration (FDA) receives between 100 and 150 new drug applications (NDAs) per year and approves approximately 60 percent of them (DiMasi, Hansen, and Grabowski 2003).

Regulatory agencies are subject to different formal policies, which focus primarily on timeliness of review. Reviewers at the FDA are evaluated by the proportion of applications that are resolved on time: within 300 days for regular review and 180 days for priority review. At the European Medicines Agency (EMA) in the European Union, these targets are 210 and 150 days; at the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), meanwhile, they are 360 and 270 days. To the best of our knowledge, there are no formal rules regarding how many drugs a country's regulatory agency needs to approve within a given year, although, informally, the agencies often publicize their output. In the United States, for example, the FDA often emphasizes the number of drugs it has been able to approve when seeking its annual Congressional budget appropriation (see online Appendix Exhibit 1). The FDA reports its drug approval output by fiscal year, which ends in September. Therefore, if regulators perceived a quota associated with approvals output, we would expect to see output surges at the end of September rather than at the end of December.

We provide more information on the drug approval processes in the European Union, China, Japan, South Korea, and the United States in online Appendix A. Online Appendix B provides a theoretical model of drug approvals in which regulators trade off acquiring better information against facing costly delays.

II. Data

We conduct our analysis in three parts. First, we use a broad international sample to look at output surges in drug approvals by calendar date. For this analysis, our data come from the United States, the European Union, the United Kingdom, Japan, China, and South Korea. Second, we examine adverse effects associated with drugs approved during output surges. For this analysis, we use data on adverse events reported from the United States and European Union. Finally, we provide supporting evidence on mechanism and robustness; for this analysis, we use data on application dates and more detailed adverse effects from the United States.

A. *Drug Approvals*

Our sample contains drug application information for the following country or regional regulatory agencies: the United States, the European Union, the United Kingdom, Japan, China, and South Korea. For the US data, we use data provided by the FDA.[6] We focus on new drug applications (NDAs and biological license applications, or BLAs) between January 1980 and September 2016.[7] For each approved NDA, we collect the drug's approval date, its review classification

[6] We download these data from https://www.accessdata.fda.gov/scripts/cder/daf/.
[7] We use the abbreviation "NDA" throughout to refer to both NDAs and BLAs.

(standard versus priority review), and its disease indication as measured by the International Classification of Diseases codes (ICD-9).[8] Our sample includes 3,312 unique NDAs, of which 636 have a priority review designation. For NDAs that have multiple approval dates, we use the first approval date indicated in the database. Additionally, we hand collect application dates for 1,890 NDAs using dates found in NDA approval letters (available after 1998).

Remaining drug approvals data come from the Clarivate Analytics Cortellis Investigational Drugs database between January 1980 and June 2014. In our analysis, we focus on 4,871 drug approvals from the countries in our data that have the highest number of drug approvals. This includes approvals from the central EU authority (the EMA) and several country-level authorities within the European Union (Germany, France, Spain, and Portugal) as well as the United Kingdom, Japan, China, and South Korea. We code a drug's approval date within a given country as the first date on which it is listed as registered or launched in that country.

B. *Adverse Events*

Adverse effects can be reported by the manufacturer of the drug, physicians, and consumers and can provide a fine-grained measure of safety across drugs. Adverse events data are available only from the United States and European Union.

In the United States, we record adverse drug reactions (ADR) from the FDA Adverse Event Reporting System database (2012–2016) and its predecessor, the Legacy Adverse Event Reporting System (2004–2012). Each ADR event contains information about the seriousness of the adverse effect: whether it involved death, life-threatening injury, hospitalization, disability or permanent damage, or a congenital anomaly/birth defect. In cases where an adverse reaction report is linked to multiple drugs, we link the event to the drug listed as the "primary suspect."

We use adverse effects data for EU countries, as measured in EudraVigilance, the EMA's database of suspected ADR reports (http://www.adrreports.eu/en/). The EudraVigilance system captures adverse drug reports from across the European Union; our EU adverse effects data include reports from all of its member states. In EudraVigilance, a typical record contains the number of adverse effect events, summed up across all countries in the European Economic Area. We are unable to see the details of reported cases from the European Union; for that reason, our main adverse effects analyses compare total adverse effects in both the United States and the European Union. In supplementary analyses, we will use additional information about the seriousness of the adverse event found in the US data.

There are several limitations to the use of adverse events data as a measure of safety. As Baciu, Stratton, and Burke (2007) note, adverse events data may suffer from underreporting bias or recall bias and may exclude cases in which there is poor case documentation. More critically, popular drugs are likely to have more reported adverse events simply because more people are using them. In our online Appendix, we report results from the United States that include controls for direct measures

[8] A drug is often matched to more than one ICD-9. We include all drug-ICD-9 matches.

of the popularity and usage of the drug, employing data from the US Medicare Expenditure Panel Survey.

III. Main Results

A. *Analysis of Number of Approvals*

Panels A and B of Figure 1 illustrate our first key finding: across the world, more drugs are approved in December than in any other month. Panel A illustrates results from the United States and plots the total number of drug approvals in our sample period by month and, within a month, by whether they are approved in the first, middle, or last ten days of the month. We find that December approvals account for over 15.07 percent of all approvals, or about 7.35 percent ($t = 5.26$) more than the average in other months. Similarly, panel B presents results from our international sample, which includes the European Union, United Kingdom, Japan, China, and South Korea. December approvals account for 21.06 percent of all approvals in this sample, or 13.89 percent ($t = 7.41$) more than the average in other months.

Panels A and B of Figure 1 also show that there are more approvals during another natural desk-clearing window: month-ends. In the United States, 45.50 percent more drugs are approved on days that fall in the last 10 days of a month than in any other given period ($t = 9.36$). In our international sample, this ratio is 50.50 percent ($t = 6.17$). Online Appendix Table A1 presents the accompanying regression results, which show that these output surges are statistically significant and robust to inclusion of a variety of controls.

If our results are driven by the idea that such dates serve as natural psychological markers of production period-ends, then we may expect to see similar behavior associated with holiday breaks. In the United States, Thanksgiving is the most celebrated holiday outside of Christmas and is associated with a long travel weekend. Panel C of Figure 1 confirms this fact: on average, more drugs are approved the week before Thanksgiving than in any other (non-December) week in the United States. This pattern, however, does not hold outside the United States, where the week before Thanksgiving has, if anything, slightly fewer approvals than other non-December weeks. Similarly, panel D shows that the same idea holds for Lunar New Year, which is widely celebrated in China, Japan, and South Korea but not in the United States or European Union. Here, we see a spike in approvals the week before Lunar New Year only in Asian countries and not in the United States or European Union. Online Appendix Table A2 presents the accompanying regression results.

B. *Adverse Effects*

Collectively, our results thus far show that there are consistently more drugs approved at regular calendar benchmarks. If this is the result of rushed review, then we might expect drugs approved during these periods to have more safety issues. To test this hypothesis, we estimate the following set of regressions:

$$(1) \qquad AdverseEffects_{ik} = a_0 + a_1 ApprovedPeriod_i + X_{ik} + \delta_k + e_{ik}.$$

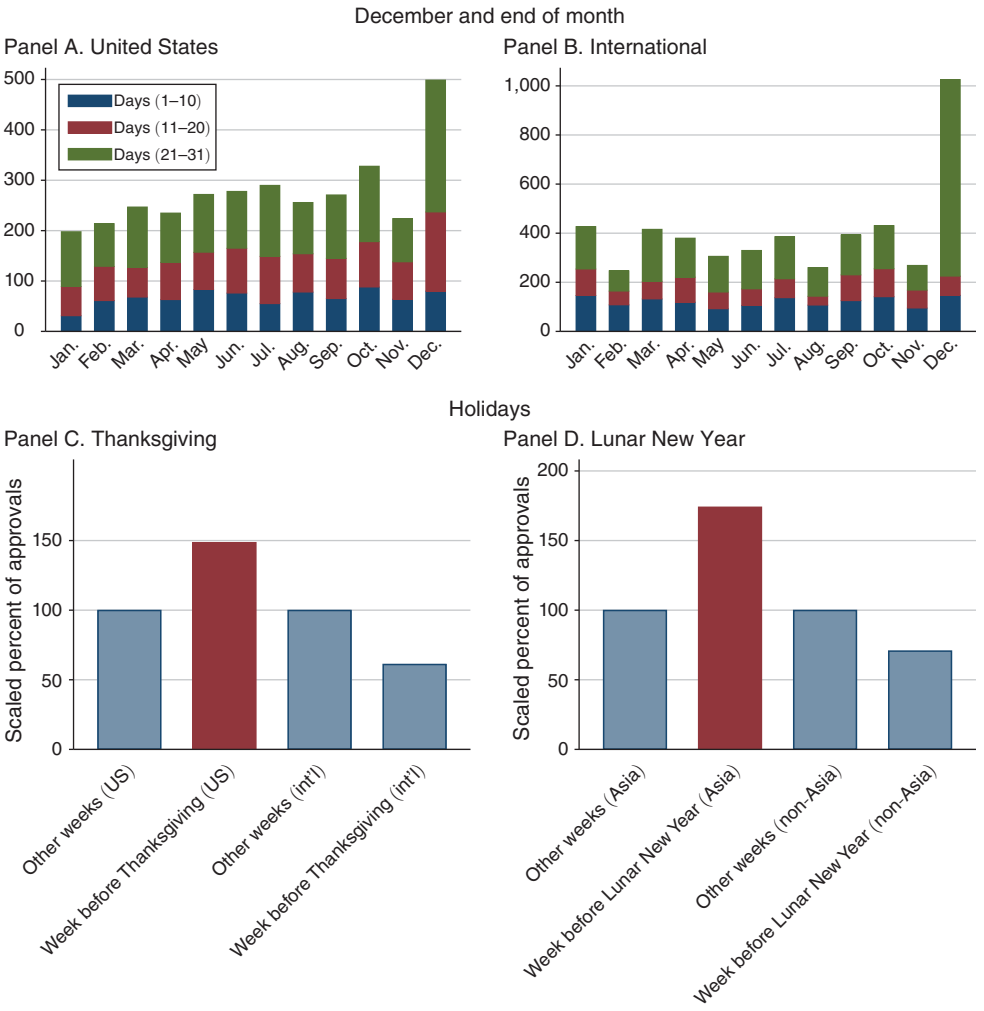

FIGURE 1. NUMBER OF DRUG APPROVALS

Notes: In panel A, we plot the total number of drugs approved in each month by ten-day bin for drugs approved in the United States between January 1980 and September 2016. In panel B, we plot the total number of drugs approved internationally (that is, in the European Union, the United Kingdom, Japan, China, and South Korea) in each month by ten-day bin, between January 1980 and June 2014. In the first two bars of panel C, we compare the number of approvals in the United States during the week before Thanksgiving with average approvals in other weeks of the year in the United States, excluding December. In the last two bars, we report the average number of approvals during the same periods in non-US countries. Similarly, the first two bars of panel D compare the number of approvals in the week before Lunar New Year in Asian countries (China, Japan, and South Korea) with the average number of weekly approvals in other weeks of the year in these countries, excluding December. The last two bars of panel D show this same comparison in non-Asian countries (the United States, European Union, United Kingdom). In both panels C and D, approvals are scaled to a value of 100 in the control (nonholiday) sample.

Each observation is a drug (i)-disease indication (k). The coefficient of interest is a_1, which asks whether drugs approved in certain periods have more safety issues. Our standard errors are clustered at the disease level.

In panel A of Table 1, we show that drugs approved during December output surges are associated with more adverse effects, in both the United States and

TABLE 1—ADVERSE EFFECTS, DECEMBER AND END-OF-MONTH DRUGS

Variables	log(1 + adv.) US (1)	log(1 + adv.) US (2)	log(1 + adv.) EU (3)	log(1 + adv.) EU (4)
Panel A. December				
December	0.249	0.207	0.0600	0.168
	(0.0832)	(0.106)	(0.0318)	(0.0573)
Observations	9,389	7,189	16,051	15,298
R^2	0.246	0.454	0.533	0.724
ICD-9 × year fixed effects		Yes		Yes
Country × year fixed effects				Yes
Panel B. End of month				
Last ten days	0.188	0.214	0.0461	0.0789
	(0.0563)	(0.0708)	(0.0206)	(0.0413)
Observations	9,389	7,189	16,051	15,298
R^2	0.246	0.454	0.534	0.724
ICD-9 × year fixed effects		Yes		Yes
Country × year fixed effects				Yes

Notes: In this table, we examine the adverse effects associated with end-of-year and end-of-month drugs. In columns 1 and 2 of both panels, observations are at the drug-disease level (disease measured using ICD-9 codes) within the United States, with sample counts taking into effect dropped singleton observations. A drug can be linked to multiple ICD-9s. In columns 3 and 4 of both panels, observations are at the country-drug-ICD-9 level for all EU countries. US and EU adverse effects are described in Section II of the text. Standard errors are clustered at the ICD-9 level. Robust standard errors in parentheses.

European Union. Focusing on columns 2 and 4, which include year of approval by disease (ICD-9) fixed effects as well as country by year controls, we find that drugs approved in December have about 20 percent more reported adverse effects. In panel B, we show that a similarly sized correlation holds for end-of-month approvals. Online Appendix Table A3 shows that these results are robust to a levels and Poisson functional form assumption.

In Table 2, we show that a similar pattern holds for holidays: we see elevated adverse effects associated with drugs approved the week before Thanksgiving in the United States but not in the European Union. Similarly, we see no evidence of elevated adverse effects for drugs approved the week before Lunar New Year in either the United States or the European Union.[9]

As noted earlier, a key concern with interpreting adverse events data is that it does not take into account the proportion of use cases that do not generate adverse events. A safe and popular drug may generate more adverse effects than a dangerous drug simply because it is used by more people. If drugs approved in December were simply more popular, then we may mistakenly conclude that December drugs are more dangerous. In online Appendix Table A4, we show that controlling for measures of market size in the United States does not impact our findings: we still see elevated adverse effects in December, at the end of the month, before Thanksgiving, and not before Lunar New Year. Finally, online Appendix Table A5 shows that our results hold when we consider serious adverse effects only: those associated with

[9] Ideally, we would test the main effect on adverse events in Asia as well, but as previously mentioned we do not have adverse events data reported from Asia.

Table 2—Holiday Adverse Effects

Variables	log(1 + adv.) US (1)	log(1 + adv.) EU (2)	log(1 + adv.) Pooled (3)
Week before Thanksgiving	0.890	−0.317	
	(0.291)	(0.171)	
Week before Lunar New Year			0.0146
			(0.187)
Observations	7,189	15,298	23,868
R^2	0.459	0.729	0.553
ICD-9 × year fixed effects	Yes	Yes	Yes
Country × year fixed effects		Yes	Yes

Notes: In this table, we examine the adverse effects associated with drugs approved before holidays. In column 1, observations are at the drug-disease level (disease measured using ICD-9 codes) within the United States, with sample counts taking into effect dropped singleton observations. A drug can be linked to multiple ICD-9s. In column 2, observations are at the country-drug-ICD-9 level for all EU countries. In column 3, observations are at the country-drug-ICD-9 level for all EU countries plus the United States. US and EU adverse effects are described in Section II of the text. Lunar New Year occurs on a different calendar date in each year; we capture this and examine approvals in the seven days before each year-specific Lunar New Year date. Standard errors are clustered at the ICD-9 level. Robust standard errors in parentheses.

hospitalizations, disability, and, especially, with deaths. Because disaggregated data on adverse effects are only available in our US sample, online Appendix Table A5 is restricted to the United States and also includes controls for the market size variables used in online Appendix Table A4.

Our results so far are consistent with the idea of some kind of behavioral "desk clearing" in advance of natural calendar-year benchmarks. If this were the case, then we might expect more pronounced effects when regulators face a larger end-of-year workload. In particular, when regulators have been less "productive" in terms of approving drugs earlier in the year, they may feel more pressure to rush decisions in December. To test this, we use the share of drugs approved in December for a given year as a proxy for regulators' workloads during December and then examine the relationship between December workloads and adverse effects associated with December approvals. Table 3 shows that when a greater share of drugs are approved in December, the average number of adverse events associated with each December drug increases. Column 2 reports, for example, that a one standard deviation (9 percentage point) increase in the share of all drugs approved in December is associated with a 10 percent increase in reported adverse effects in the United States. Column 4 finds similar magnitudes in the European Union. Although we do not observe the total number and timing of drug applications, this provides suggestive evidence that when regulators' workloads are relatively high, drugs that go on to generate more safety problems are more likely to be approved.

C. *Alternative Interpretations*

Our results are consistent with regulators engaging in lax review in a rush to meet internal production benchmarks. However, there are several other possible interpretations for our results.

Table 3—Adverse Effects, by December Workload

Variables	log(1 + adv.) US (1)	log(1 + adv.) US (2)	log(1 + adv.) EU (3)	log(1 + adv.) EU (4)
December workload	2.293	−0.256	1.292	−0.396
	(1.209)	(0.110)	(1.551)	(0.164)
Dec. workload × Dec. drug		1.186		1.250
		(0.553)		(0.514)
Observations	545	4,856	259	2,073
R^2	0.057	0.001	0.061	0.005
ICD-9 × cohort year fixed effects	Yes	Yes	Yes	Yes
Total approvals	Yes	Yes	Yes	Yes

Notes: In this table, we examine the adverse effects associated with December drugs, interacted with the amount of work regulators likely had in that year. The level of analysis is a drug-disease observation (a drug can be linked to multiple ICD-9s). US and EU adverse effects are described in Section II of the text. In columns 1 and 3, observations are limited to drugs approved in December only. In columns 2 and 4, we expand to include all drugs, with an indicator for December drugs. December workload refers to the share of a calendar year's drug approvals that are approved in December. Total approvals refer to fixed effects for each decile of total drug approvals for that calendar year. Standard errors are clustered at the ICD-9 level. Robust standard errors in parentheses.

Strategic Timing of Review.—One possibility is that regulators collect their most complex cases throughout the year to be considered at the end of the month or the end of the year. In this case, the increased incidence of safety issues that we document may reflect the nature of the drugs themselves rather than the quality of the decision-making process that led to their approval.

To address this, we first note that our results in online Appendix Table A4 on the US sample show that the phenomenon we document cannot be explained by potential differences in disease indication, market size, or priority status between drugs approved at the end of the year or end of the month compared with those approved at other times. If December or end-of-month drugs are indeed different on some dimension, that dimension does not appear to be correlated with disease type, market size, or US priority review status. In online Appendix Table A6, we further examine whether December and end-of-month drugs differ in their novelty. If novel drugs are riskier or more difficult to assess, then it is possible that they may independently have more safety problems. We consider two measures of novelty. Following Krieger, Li, and Papanikolaou (2018), we define a chemically "novel" drug as one that is molecularly distinct from drug candidates that have previously entered development. We also define a drug as novel if it is the first to focus on a particular biological target (e.g., the first to bind to a particular protein). Online Appendix Table A6 shows that neither December nor end-of-month drugs differ in their novelty.

Strategic Timing of Applications.—Another possibility is that the approval patterns we see are driven by an antecedent surge in applications. If firms believe that their application is more likely to receive a lax review in a backed-up year-end docket, they may be more likely to time their submissions so that their most dangerous drugs are expected to be evaluated in December. The US Prescription Drug

User Fee Act (PDUFA) of 1992 instituted targets for timely review. As a result, FDA regulators were evaluated on the percentage of priority and regular applications that were reviewed within six and ten months, respectively. Carpenter et al. (2012) documented that these deadlines did in fact lead to spikes in the number of drugs approved at six and ten months exactly. If firms wished to time their applications so that they are "due" in December, then they would want to submit regular review applications in February and priority review applications in June.

To test this, we collect data on application dates for approved drugs, which are available for US approvals after 1998. We then generate a "synthetic" cohort of drugs that would be approved in each month, assuming that applications are evaluated on time. In Table 4, we show that approved drugs submitted so that their expected approval date is December do not appear to generate more adverse effects; if anything, drugs submitted with expected December review dates have point estimates indicating they may be marginally safer (though insignificantly so). These results suggest that the increase in adverse events associated with actual December drugs cannot be attributed to the characteristics of drugs with expected December review dates.

IV. Discussion and Welfare

The results of our analysis suggest that regulators approve more drugs at the end of the year and before month-ends and holidays and that drugs approved during these time periods are associated with a significantly higher rate of follow-on adverse effects. These results may be surprising because the stated goal of regulatory agencies across the globe is to adjudicate the safety and efficacy of drug candidates, not to simply generate more approvals. This raises the natural question of why regulators appear to respond to natural behavioral deadlines by quickly approving more drugs, instead of quickly rejecting them.

We believe that there are several reasons why the behavior of drug reviewers may not be symmetric when it comes to approvals and rejections. First, even though regulators are not formally incentivized on the basis of approval counts, they are often informally evaluated on this metric. For example, panel A of Exhibit 2 in the online Appendix links to a report by the former FDA commissioner, Scott Gottlieb, highlighting the productivity of the FDA as measured by number of approvals. Similarly, panel B links to how public discourse related to the FDA's productivity is also often based on comparing approval output.

Relatedly, while it is easy to point to a drug approval as evidence of productivity, it is much harder to take credit for the decision to reject a drug because policymakers never observe the counterfactual adverse effects that this drug may have generated. Further, because safety withdrawals and high-profile black box warnings are relatively rare and generally take place years after a drug goes on the market, the downside realizations of drug approval tend to only be revealed with a lag. For similar reasons, rejection decisions are likely to be met with immediate resistance from firms, and possibly from patients as well, but fewer parties are as likely to be invested in opposing approvals because the costs of unsafe approvals are not immediately salient. Further, despite low success rates in drug development overall, the majority (around 60 percent) of NDAs are approved (conditional on successful

TABLE 4—STRATEGIC TIMING OF APPLICATION SUBMISSION: US SAMPLE

Variables	Synt. approvals (1)	Synt. approvals (2)	log(1 + synt. adv.) (3)	log(1 + synt. adv.) (4)
Synthetic December	0.002	0.002	−0.106	−0.130
	(0.007)	(0.007)	(0.144)	(0.205)
Observations	44,323	44,323	5,197	4,012
R^2	0.176	0.359	0.252	0.439
ICD-9 × year fixed effects		Yes		Yes

Notes: In this table, we examine whether a surge in December approvals is driven by the timing of applicants' decisions to submit NDAs. The level of analysis in columns 1 and 2 is a year-month-disease observation, and the sample is restricted to US approvals after 1998. Synthetic December refers to a drug's application plus 10 months if it is a regular review application or its application date plus six months if it is a priority review application. Synthetic approvals refers to the number of approvals in a given year-month-disease category if all applications were approved at their deadline (six months from submission in the case of priority applications and ten months from submission in the case of regular applications). In columns 3 and 4, observations are at the drug-disease level. Synthetic adverse effects refers to adverse effects associated with the drugs, with synthetic approval dates calculated based on their application dates. Standard errors are clustered at the ICD-9 level. Robust standard errors in parentheses.

phase III trials). This may shift the default stance of regulators from rejection to approval.

Lastly, we consider the welfare implications of these documented approval surges. Our results imply substantial costs associated with rushed approvals—in the form of increased safety issues. However, a welfare analysis also needs to take into account the potential benefits of a more lax review—such as the patients helped by the approved drug (who do not suffer from adverse events) and the potential follow-on medications that might be developed as a result—which we are unable to fully account for in our tests.

That said, we can use our data on adverse effects to perform a back-of-the-envelop calculation regarding the dollar costs associated with the adverse effects arising from the "desk-clearing" behavior we document. This can be thought of as a lower bound to what the benefits of rushed review must be in order to make up for the elevated incidence of adverse safety effects.

To estimate this, we take the increased adverse effects we estimate, translate them into a quality-adjusted life year (QALY) measure, and then assign a dollar value to these. This requires that we make several assumptions regarding the relevant counterfactual, the QALYs associated with an adverse effect, and the value of a statistical life (VSL). We attempt to take a conservative estimate on all of these dimensions:

(i) We assume that all "extra" drugs that are approved in December would have still been approved but that their review would have been more rigorous (e.g., more careful drug labeling and dosage recommendations) so that they would have the average number of adverse effects associated with drugs approved at other times of the year. This means that we only consider the marginal excess adverse effects associated with December drugs (rather than assuming that these drugs would not have been approved at all, in which case we would include all their associated adverse events into our count of excess adverse events).

(ii) We only associate an adverse effect with a drug if that drug is the "primary suspect" for that effect.

(iii) Because it is difficult to specify what a "disability" or "hospitalization" means in QALY terms, we assume that the only adverse events of consequence are deaths.

(iv) We use a relatively conservative VSL measure. This measure, $885,000 in 2020 dollars, comes from actual payouts.[10]

To calculate this figure, we begin with the fact that December drugs are associated with, on average, approximately 20 percent (Table 1, column 2) more adverse effects than comparable drugs approved at other times. Further, we have that, on average, 77 drugs are approved in December each year in the United States and European Union, and the average number of adverse effects associated with non-December approvals is approximately 1,200 per drug. A 20 percent increase would therefore translate into approximately 18,500 excess adverse effects. To translate this adverse effects figure into QALYs, we note that, in the United States (where we have data on types of adverse effects), roughly 7.6 percent of adverse effects are deaths. Applying this figure implies approximately 1,400 lives lost per year due to rushed review in the United States and European Union; multiplying by the VSL of $885,000 per life gives a total loss estimate of roughly $1.2 billion per year.

In online Appendix Table A7, we consider a range of additional plausible scenarios.

These imply between 1,400 and 9,000 lives lost per year, or total losses of up to $8 billion per year over our sample period due to rushed review.

V. Conclusion and Policy Considerations

Stepping back, given the global surge in drug approvals ahead of informal deadlines, and the incremental adverse effects and costs associated with these drugs, we face the question of what types of policies could address this seeming desk-clearing behavior. As we mention above, while there are potential benefits to more lax review as a broad policy, it is unlikely that an optimal policy response would be a targeted loosening of review solely at a given calendar date (e.g., just before Thanksgiving). Instead, drug regulators could adopt a broader loosening of criteria or constraints (Isakov, Lo, and Montazerhodjat 2019). Such a policy would *not* produce the approval surges at specific calendar dates across all drugs (irrespective of disease class, market size, etc.) that we see in the data.

In fact, we view one of the key aspects of the paper as encouraging researchers and policymakers to think about how to design policies to deal with non-policy-induced inefficiencies, being true even if we cannot offer a perfectly optimal policy "solution."

[10] Although the estimated value of a life in the literature has ranged significantly based on study and context—getting upward of ten million dollars per life—we focus on values used in federal payout programs. We take the low end of this range, using the value established during the Nixon administration ($885,000 in 2020 dollars), with one of the most recent by the 9/11 Commission of roughly $975,000 yielding similar results (Appelbaum 2020).

Past literature has suggested ways to address bunching before *formal* deadlines, such as Liebman and Mahoney (2017) and Oyer (1998). These proposed solutions include using deliberately scheduled audit timing and deadline grace periods, which could potentially help attenuate formal deadlines' impact on behavior. Although they do not perfectly fit our setting, this literature suggests two potential ways to address the safety issues we document. First, policymakers could impose a smoothing function over time. For example, regulators could require that the number of drugs approved in a given month cannot be more than twice the average of the preceding 11 months. Another approach would be to create a "holding tank" for approvals made at year-end, month-end, or just prior to long holiday breaks. Instead of being immediately cleared for marketing approval, drugs approved during these periods would undergo one final reevaluation subsequent to the salient informal deadline (say, early January). While imperfect, these policies have the potential to unwind aspects of the desk-clearing behavior we document, and they do so in ways that are relatively low cost and simple to implement.

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Internal Deadlines, Drug Approvals, and Safety Problems Online Appendix

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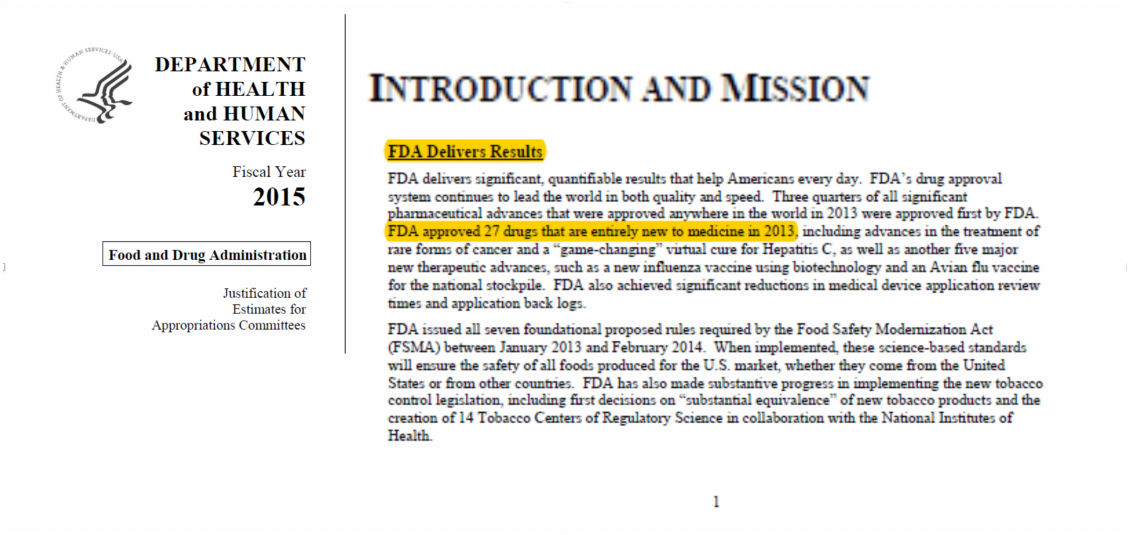
Appendix Exhibit 1



DEPARTMENT of HEALTH and HUMAN SERVICES

Fiscal Year **2015**

Food and Drug Administration

Justification of Estimates for Appropriations Committees

INTRODUCTION AND MISSION

FDA Delivers Results

FDA delivers significant, quantifiable results that help Americans every day. FDA's drug approval system continues to lead the world in both quality and speed. Three quarters of all significant pharmaceutical advances that were approved anywhere in the world in 2013 were approved first by FDA. FDA approved 27 drugs that are entirely new to medicine in 2013, including advances in the treatment of rare forms of cancer and a "game-changing" virtual cure for Hepatitis C, as well as another five major new therapeutic advances, such as a new influenza vaccine using biotechnology and an Avian flu vaccine for the national stockpile. FDA also achieved significant reductions in medical device application review times and application back logs.

FDA issued all seven foundational proposed rules required by the Food Safety Modernization Act (FSMA) between January 2013 and February 2014. When implemented, these science-based standards will ensure the safety of all foods produced for the U.S. market, whether they come from the United States or from other countries. FDA has also made substantive progress in implementing the new tobacco control legislation, including first decisions on "substantial equivalence" of new tobacco products and the creation of 14 Tobacco Centers of Regulatory Science in collaboration with the National Institutes of Health.

1

The FDA must appear before Congress each year to request a budget for the upcoming year. For instance, this is taken from the 2015 Congressional Budget Justification Document that they used in this request. They mention the number of drugs approved in the "FDA Delivers Results" section on page 1.

Appendix Exhibit 2

2018 Statement from FDA Commissioner Scott Gottlieb

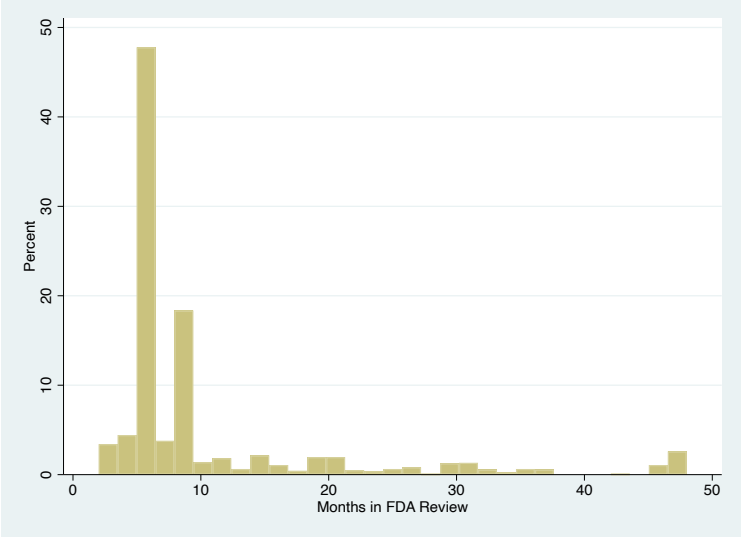
Panel A. Above is a link to a report by the then-Commissioner of the FDA (Scott Gottlieb) in December 2018 touting the record number of new drug approvals.

FDA Touts Strong Drug Approval Performance in 2014

Panel B. Above is a link to a media report reflecting on then-Commissioner of the FDA (Margaret Hamburg)'s blog posting on new drug approvals in 2014.

Appendix Figure 3: Time in Review, Approved drugs

A. Priority Drugs



B. Non-Priority Drugs

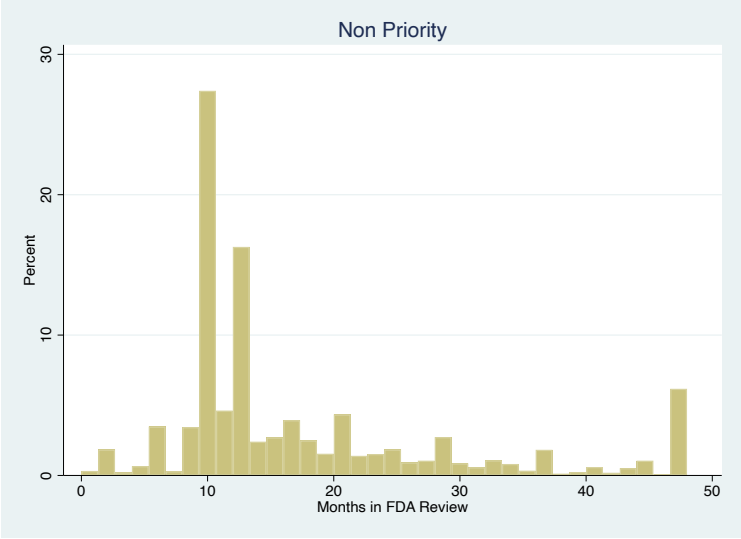


Table A1: Approvals in December and End of Month

VARIABLES	(1) Approvals US	(2) Approvals Int'l	(3) Approvals US	(4) Approvals Int'l
December	2.317***	1.339***	0.0853***	0.161***
	(0.441)	(0.181)	(0.0290)	(0.0330)
Last 10 Days	1.371***	0.606***	0.0273**	0.0285***
	(0.146)	(0.0982)	(0.0105)	(0.0105)
Observations	1,323	6,210	4,938	8,200
R-squared	0.206	0.144	0.306	0.276
Year FE	YES	YES		
Country FE		YES		YES
ICD-9 x Year FE			YES	YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: In this table, we examine the number of approvals associated with December and end-of-month drugs. Column 1 focuses on US approvals, with observations at the year-"month-bin" level (each month is divided into three bins: days 1–10, 11–20, and 21–end of month). Column 3 focuses on US approvals as well, but controlling for disease by time effects, as proxied by ICD-9 codes. To do this, we expand the level of observation to be at the ICD-9-year-month bin level (a drug can be associated with multiple ICD-9s). Columns 2 and 4 repeat this exercise for an international sample comprising of approvals in the EU, UK, Japan, China, and South Korea. Observations in Column 2 are at the country-year-month bin level; Column 4 adds controls for disease trends so that observations are at the country-year-month bin-disease level. *December* is an indicator variable that takes a value of one if the drug is approved in December, and zero otherwise. *Last 10 Days* is an indicator variable that takes a value of one if the drug is approved is the last bin of any month. Standard errors in Columns 1 and 2 are clustered at the year level; standard errors in Columns 3 and 4 are clustered at the ICD-9 level.

Table A2: Approvals before Holidays

VARIABLES	(1) Approvals US	(2) Approvals Int'l	(3) Approvals Asia	(4) Approvals non-Asia
Week bf. Thanksgiving	0.781***	-0.180***		
	(0.287)	(0.0409)		
Week bf. Lunar New Year			0.337*	-0.270**
			(0.177)	(0.0997)
Observations	1,738	9,114	4,087	4,843
R-squared	0.098	0.136	0.098	0.211
Year FE	YES	YES	YES	YES
Country FE		YES	YES	YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: In this table, we examine the number of approvals associated with holiday periods. The unit of observation is calendar-week. *Week bf. Thanksgiving* is an indicator variable that takes a value of one if the drug is approved in the seven-day period before Thanksgiving Day in the US. *Week bf. Lunar New Year* is an indicator variable that takes a value of one if the drug is approved in the seven-day period before Lunar New Year. The sample covers all non-December approvals between January 1980 and September 2016 in the US, and between January 1980 and June 2014 in other countries (i.e., EU, UK, China, Japan and South Korea). Standard errors are clustered the year level.

Table A3: Adverse Effects, December and End-of-Month Drugs

(A) December

VARIABLES	(1) Adverse US	(2) Adverse EU	(3) Adverse Poisson US	(4) Adverse Poisson EU
December	2,642***	63.32***	0.726***	0.149
	(747.8)	(18.24)	(0.0798)	(0.0938)
Observations	7,189	15,298	9,389	16,051
R-squared	0.362	0.444		
ICD-9 x Cohort Year FE	YES	YES		
ICD-9, Cohort Year, Country FE			YES	YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

(B) End-of-Month

VARIABLES	(1) Adverse US	(2) Adverse EU	(3) Adverse Poisson US	(4) Adverse Poisson EU
Last 10 Days	1,433***	21.88**	0.371***	0.101
	(417.5)	(10.45)	(0.0634)	(0.0626)
Observations	7,189	15,298	9,389	16,051
R-squared	0.360	0.443		
ICD-9 x Cohort Year FE	YES	YES		
ICD-9, Cohort Year, Country FE			YES	YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: In this table, we examine the adverse effects associated with end-of-year and end-of-month drugs. The level of analysis is a drug-disease observation (a drug can be linked to multiple ICD-9s). US and EU adverse effects are described in Section 2 of the text. Standard errors are clustered at the ICD-9 level.

Table A4: Adverse Effects with Market Size Controls, US sample

VARIABLES	(1) Log(1+Adv)	(2) Log(1+Adv)	(3) Log(1+Adv)	(4) Log(1+Adv)
December	0.345***			
	(0.0805)			
Last 10 Days		0.173***		
		(0.0559)		
Week bf. Thanksgiving			1.172***	
			(0.145)	
Week bf. Lunar New Year				0.290
				(0.247)
Observations	9,224	9,224	9,224	9,224
R-squared	0.364	0.364	0.367	0.363
Full Drug Level Controls	YES	YES	YES	YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: In this table, we examine the adverse effects associated with end-of-year and end-of-month drugs. The level of analysis is a drug-disease observation (a drug can be linked to multiple ICD-9s). Full controls include controls for: fixed effects for ICD-9 and drug cohort (based on a drug's year of approval), an indicator for a drug's priority status, fixed effects for a drug's decile in terms of market size as measured by its number of prescriptions in the MEPS data, and fixed effects for the decile of the number of generic applications that we also approved in that month (to capture the FDA's workload for non-NDA approvals). For drugs for which we are unable to match this information, we include an indicator for missing information and set the values of these figures to zero. Standard errors are clustered at the ICD-9 level.

Table A5: Disaggregated Adverse Effects with Market Size Controls, US sample

VARIABLES	(1) Log(1+Death)	(2) Log(1+Death)	(3) Log(1+Death)	(4) Log(1+Death)	(5) Log(1+Serious)	(6) Log(1+Serious)	(7) Log(1+Serious)	(8) Log(1+Serious)
December	0.216***				0.256***			
	(0.0737)				(0.0806)			
Last 10 Days		0.0897*				0.148***		
		(0.0502)				(0.0548)		
Wk bf. Thanksgiving			1.183***				1.159***	
			(0.142)				(0.140)	
Wk bf. Lunar New Year				0.511**				0.504**
				(0.214)				(0.225)
Observations	9,224	9,224	9,224	9,224	9,224	9,224	9,224	9,224
R-squared	0.376	0.375	0.380	0.376	0.371	0.370	0.374	0.370
Full Drug Level Controls	YES	YES	YES	YES	YES	YES	YES	YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: In this table, we examine the adverse effects associated with end-of-year and end-of-month drugs. The level of analysis is a drug-disease observation (a drug can be linked to multiple ICD-9s). Full controls include controls for: fixed effects for ICD-9 and drug cohort (based on a drug's year of approval), an indicator for a drug's priority status, fixed effects for a drug's decile in terms of market size as measured by its number of prescriptions in the MEPS data, and fixed effects for the decile of the number of generic applications that we also approved in that month (to capture the FDA's workload for non-NDA approvals). For drugs for which we are unable to match this information, we include an indicator for missing information and set the values of these figures to zero. Standard errors are clustered at the ICD-9 level.

Table A6: Are December Drugs Harder to Examine?

(A) December

VARIABLES	(1) Nov. Drug US	(2) Nov. Drug Int'l	(3) New Target US	(4) New Target Int'l
December	-0.00500	-0.00321	-0.00570	0.0298
	(0.0212)	(0.0402)	(0.0214)	(0.0352)
Observations	5,772	15,374	3,918	12,078
R-squared	0.423	0.797	0.543	0.814
Cohort Year X ICD-9 FE	YES	YES	YES	YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

(B) End of Month

VARIABLES	(1) Nov. Drug US	(2) Nov. Drug Int'l	(3) New Target US	(4) New Target Int'l
Last 10 Days	0.0252*	0.0305	-0.00658	0.0204
	(0.0151)	(0.0244)	(0.0137)	(0.0263)
Observations	5,772	15,374	3,918	12,078
R-squared	0.424	0.797	0.543	0.814
Cohort Year X ICD-9 FE	YES	YES	YES	YES

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Notes: In this table, we examine the adverse effects associated with end-of-year and end-of-month drugs. The level of analysis is a drug-disease observation (a drug can be linked to multiple ICD-9s). *Novel Drug* is a measure of drug novelty (see Krieger, Li and Papanikolaou [5]) that is based on the chemical similarity between the new drug and existing drugs; the measure is a dummy variable that takes a value of one if the drug's molecular similarity to existing drugs is less than 33%. *New Target* refers to whether a drug is the first drug in its ATC seven-digit class. Standard errors are clustered at the ICD-9.

Table A7: Cost of Rushed Review: Magnitude Estimates

Panel A): Assuming all December Drugs would eventually be approved, and thus there is solely a cost of incremental adverse effects on all December Drugs from rushed review

	Primary Suspect Only	**Any Suspect**
Additional Adverse Effects Per Year	18,562	19,480
Additional Deaths Per Year	1,416	1,452
Total Extra Costs Per Year	$1,253,014,611	$1,284,583,751

Panel B): Assuming the excess December Drugs approved (relative to the prior 11-month average) were mistakes from rushed approval, so all of the adverse effects on these "excess" December Drugs are incremental

	Primary Suspect Only	**Any Suspect**
Additional Adverse Effects Per Year	103,903	107,889
Additional Deaths Per Year	7,925	8,039
Total Extra Costs Per Year	$7,014,039,544	$7,114,430,497

Panel C): As in Panel B, assuming "excess" December Drugs were mistakes from rushed approval, so all of the adverse effects on these excess December Drugs are incremental, along with imposing extra errors on all other December Drugs due to rushed review, increasing their adverse effects (according to Panel A estimates)

	Primary Suspect Only	**Any Suspect**
Additional Adverse Effects Per Year	122,465	127,369
Additional Deaths Per Year	9,341	9,490
Total Extra Costs Per Year	$8,267,054,155	$8,399,014,247

Notes: This table shows a range of scenarios for the magnitude estimate of the cost of rushed review. In this table, we use December Drugs (December Drugs) in the US and EU, as these are the only two regions in which we can obtain adverse effect data. While the estimated value of a life in the literature has ranged considerably based on study and context - reaching upwards of $10 million per life - we focus on values actually utilized in federal payout programs. We take the low-end of this range, using the value established during the Nixon Administration ($885,000), with one of the most recent by the 9-11 Commission of roughly ($975,000) yielding similar results. In the panels below, we show estimates of the additional Adverse Effects, Deaths, and Costs according to the scenario assumptions described in each Panel heading.

A Approvals Process

In this section, we provide some details about the drugs approvals processes in each of our sample country or regional regulatory agencies. In most cases, review agencies are responsible for carrying out four key functions: a) regulating clinical trials and setting rules for data admissibility; b) performing reviews of marketing authorizations for pharmaceuticals and medical devices; and c) collecting, analyzing, and disseminating information regarding the post-marketing safety (Ng [6]).

In recent years, most agencies also have a dual-track approvals process in which there is a priority track and a regular review track. Agencies typically set targets for how quickly reviews are done. We have found no evidence that there are any quotas based on calendar-year volume of drug approvals.

A.1 US

Before a new prescription drug can be marketed in the US, it must receive approval from the Food and Drug Administration (FDA). To receive approval, a firm must submit a new drug application (NDA) to the FDA's Center for Drug Evaluation and Research (CDER). When an NDA is filed, it is assigned to an internal review committee that is usually composed of medical officers who review all clinical trial results, pharmacology specialists who review toxicity and drug functioning, statisticians who review the quality of the drug's study protocols, chemists or biologists who focus on the manufacturing process, and a project manager who coordinates and oversees these various review activities [3].

Regulators can influence the speed of review in several ways: they can choose when to schedule meetings with review team members, decide how detailed site visits need to be, and, in some cases, also decide whether or not to convene advisory panels to seek additional input. Carpenter et al. [1], in detailing the possible mechanisms by which review deadlines could stimulate approval surges before these deadlines, argue that "drugs approved in the window just before the deadline may be less likely to receive sufficient time and expertise applied to their reviews (Huber and Kunz [4]), perhaps through curtailed advisory committee consultations or rushed drug labeling decisions, which typically occur at the end of the review process." We argue that these same mechanisms also allow regulators to rush review to meet internal benchmarks.

Since 1992, FDA review teams have also been subject to the following (non-binding) deadlines: regular NDAs should attempt to receive a decision within 10 months of

application, and a priority NDA should receive a response within six months. There are no formal rules regarding how many drugs the FDA needs to approve, although, informally, the FDA does publicize its ability to "bring more new products to market faster than ever before" [3], particularly when seeking its annual Congressional budget appropriation (see Appendix Exhibit 1). The FDA reports its drug approval output by fiscal year, which ends in September. If regulators perceived a quota associated with approvals output, we would expect to see output surges at the end of September rather than at the end of December.

A.2 EU

The European Union recognizes three different paths to drug approval: a centralized review in which a drug is evaluated by a centralized authority—the European Medicines Agency (EMA)—for approval in all EU jurisdictions; application(s) in the drug offices of individual member countries for approval in that country only; or an application to the EMA after approval in any given member state for "mutual recognition" in other EU countries [7]. For our analysis, we focus on drugs that go through the centralized EMA review, for which we have more reliable approval dates data.

To receive approval via the centralized approach, drug makers first submit a Marketing Authorisation Application (MAA), which is generally evaluated by the Committee for Medicinal Products for Human Use (CHMP), with the input of several other committees. Much like its analogue NDA in the United States, an MAA contains information on a drug's trial protocols and results to date, as well as information on its pharmacological properties and proposed manufacturing process. Once received, an MAA is assigned to two "rapporteurs," who manage the scientific team members who perform the assessment [2].

The formal timeline for EMA review is as follows: the committee has 120 days to perform an initial review and to ask any clarifying questions of the drug maker. The clock on review time is stopped as the EMA awaits a response from the drug maker, who generally has up to three months to reply. Following the drug maker's reply, the assessment committee has 90 days to come to a decision for regular applications and 30 days for priority applications. During this period, rapporteurs, like their counterparts at the US FDA, manage a team of medical, statistical, and pharmacological experts, and can also consult with external advisory councils.

As in the United States, the EMA does not have formal quotas related to calendar year output. Informally, the FDA, EMA, and other agencies are often compared against each other in terms of both drug approvals output and review times.

A.3 UK

Drug approval decisions in the United Kingdom are made by the Medicines and Healthcare Products Regulatory Agency (MHRA). Like the FDA and EMA, the MHRA is responsible for setting clinical trial regulations, reviewing drug and device applications for safety and efficacy, and monitoring post-market safety. Prior to the UK's exit from the EU, there were three tracks for drug approval: a centralized procedure in which applications were submitted to the EMA for Europe-wide marketing approval (this was the more common path), a national procedure to obtain approval in the UK only, or a mutual recognition procedure in which the UK decides whether to accept the approval decision from another EU member state (known as the "Reference Member State (RMS)"). Under the nationalized procedure, UK regulators aim to review applications within 210 days, whereas under the mutual recognition procedure regulators have 90 days to review acceptance materials from the RMS member state.

A.4 Japan

Drug approvals in Japan are handled by the Pharmaceuticals and Medical Devices Agency (PMDA). The review process in Japan is broken down into two periods. When a new drug application (NDA) is submitted, it is first reviewed by a team of regulators within the PDMA, who compile an initial set of questions. This is followed by a face-to-face "Mendan" meeting between regulators and representatives of the pharmaceutical firm to discuss these questions. The Mendan meeting typically takes place two to three months after initial submission. Following this, the next period of review is the Good Clinical Practice (GCP) compliance check, during which PDMA inspectors evaluate the key clinical trial study sites underlying the drug application, checking their raw data. Based on these meetings, the PDMA prepares a report recommending an action to the Ministry of Health, Labor, and Welfare, which makes the official approval decision.

As in the US and EU, the PMDA offers a dual-track approvals process, one for priority review drugs and one for standard review drugs. The agency is evaluated based on the percentage of applications that are reviewed on time—that is, within 360 days for standard review and 270 days for priority review.[1]

[1]See https://www.pmda.go.jp/files/000207615.pdf for additional details.

A.5 China

The National Medical Products Administration (NMPA) is in charge of all new drug registration approvals in China. Ng [6] reports that the Chinese drug approvals process is similar to that in other countries: the NMPA evaluates the completeness of the firm's application materials and, upon making this determination, forwards it to the Center for Drug Evaluation (CDE), where it is assigned to a review team that evaluates its safety and clinical claims. During this process, reviewers may interact both with the drug developer as well as with external experts. The final approval decision is based on an assessment of a drug's risk-versus-reward profile.

As is the case in other agencies, the NMPA also has a standard and priority track application process, implemented starting in 2015. Deadlines are based on time between stages of the review process (e.g., time to respond to the initial application with a first set of questions, etc.) rather than on final review time; in practice, since these reforms have taken place, priority drugs are typically reviewed within six months and non-priority drugs within 12 months.[2]

A.6 South Korea

In South Korea, applications for new drug approvals are made to the Ministry of Food and Drug Safety (MFDS), the main regulatory body for drug registration and approval. Upon receiving an application, the Drug Review Management Division (DRMD) conducts an initial pre-review, and, if accepted, the application is then subject to a more thorough review of its clinical trials, procedures and findings, as well as its compliance with manufacturing process rules and on-site inspections. Drugs for orphan or priority diseases are subject to an expedited review. As in China, review deadlines are based on time between stages of the review process; a recent study finds that, on average priority drugs are typically reviewed within 190 days and non-priority drugs within 360 days.[3]

[2]See https://www.europeanpharmaceuticalreview.com/article/98200/china-and-the-evolving-regulatory-landscape/.

[3]See http://www.koreabiomed.com/news/articleView.html?idxno=6609#:~:text=Orphan%20drugs%20totaled%2053%20in,approval%20time%20of%20361.5%20days.

B Drug Approvals with Costly Delays

In this section, we present a simple model of the drug approvals process. Consider a single regulatory body that receives applications for drug approvals. There are infinite periods: $t = 1, 2, 3, \ldots$. In each period, the regulator receives one new drug for potential approval. Drugs have an unobserved type, θ, which is equal to θ^H if a drug is safe and θ^L if it is unsafe. For each drug, the regulator observes the probability $p \in [0, 1]$ that a drug is safe.

Now, consider a drug that arrives in period $t = s$. The regulator can choose whether to approve or reject it based on its observed likelihood of being safe, p, or it can choose to delay and acquire more information. If the regulator chooses to acquire more information, it pays a cost of delay, d, and learns with certainty whether or not the drug is safe during the next period, $s + 1$. Given full information, the regulator then decides whether to approve or reject. This means that the set of drugs evaluated during period s includes the drug that arrives in period s and, possibly, the drug that arrived in period $s-1$, if its approval decision had been delayed. The regulator receives a payoff, R, for every drug that is approved, minus C if the drug turns out to be unsafe. We assume $R < C$ so that a regulator only wants to approve safe drugs. The payoff is zero if a drug is rejected.

In this model, one can think of year-ends, month-ends, and holiday breaks as representing times when the costs of delay are particularly high. That is, we assume that there are periods, $t = S$, where the cost of delay is exogenously higher, $D > d$, corresponding to deadlines, formal or informal.

This model makes the following predictions about decisions made in high versus low delay-cost periods:

Proposition B.1 *For drugs that arrive in any period t, we have the following decision rule:*

$$Decision = \begin{cases} Approve \text{ if } p > 1 - \frac{d}{c-R}, \\ Delay \text{ if } \frac{d}{R} < p < 1 - \frac{d}{c-R}, \\ Reject \text{ if } p < \frac{d}{R}. \end{cases}$$

1. *The expected quantity of drugs approved in period $t = S$ is higher than that approved in other periods $t = s$.*

2. *The expected quality of drugs approved in period $t = S$ is lower than that approved in other periods $t = s$.*

Proof Consider a drug with observed likelihood of success p. If we approve it now, we get a payoff of R from approving the drug and there is a $1-p$ chance that it will be a failure, so our expected return from approval is $R-(1-p)C$. If we delay the drug, we pay d, but then we know next period whether or not it's going to be a success for sure, so we get $pR-d$ since there's a p chance that the drug is great, and we only approve in that case so we never risk paying C. If we reject the drug, we get 0.
Regulator approves if

$$R-(1-p)C > pR-d.$$

Regulator rejects if

$$0 < pR-d.$$

So we have the following rule:

$$\text{Decision} = \begin{cases} \text{Approve if } p > 1-\frac{d}{c-R}, \\ \text{Delay if } \frac{d}{R} < p < 1-\frac{d}{c-R}, \\ \text{Reject if } p < \frac{d}{R}. \end{cases}$$

In a given period, the set of drugs coming up for consideration are (possibly) the drug that arrived last period and the drug that arrives this period. The expected likelihood of success of drugs approved is given as follows

$$\frac{E\left[p|p>1-\frac{d}{c-R}\right]\cdot\Pr\left(p>1-\frac{d}{c-R}\right)+E\left[p|\frac{d}{R}<p<1-\frac{d}{c-R}\right]\cdot\Pr\left(\frac{d}{R}<p<1-\frac{d}{c-R}\right)}{\Pr\left(p>1-\frac{d}{c-R}\right)+E\left[p|\frac{d}{R}<p<1-\frac{d}{c-R}\right]\cdot\Pr\left(\frac{d}{R}<p<1-\frac{d}{c-R}\right)}$$

The first term $E\left[p|p>1-\frac{d}{c-R}\right]$ is the average likelihood of success for drugs that are immediately approved, times $\Pr\left(p>1-\frac{d}{c-R}\right)$, the likelihood that the arriving drug falls into this range. The next term gives the likelihood of success of drugs approved that period that were delayed from $s-1$. This is just 1 because delay allows more information to be revealed, so that only successful drugs are approved. The term $\Pr\left(\frac{d}{R}<p<1-\frac{d}{c-R}\right)$ gives the likelihood that a drug would have been delayed from last period. Only a proportion of these drugs will actually turn out to be successful; this proportion is given by $E\left[p|\frac{d}{R}<p<1-\frac{d}{c-R}\right]$. Finally, this is normalized by the proportion of drugs that are approved.

Similarly, the average number of drugs approved during period s is given by

$$\Pr\left(p > 1 - \frac{d}{c-R}\right) + E\left[p|\frac{d}{R} < p < 1 - \frac{d}{c-R}\right] \cdot \Pr\left(\frac{d}{R} < p < 1 - \frac{d}{c-R}\right)$$

Now, consider a period S in which the cost of delay is higher (assume that the cost of delay in $S-1$ is still d, not D). The average quality of approved drugs is now given by

$$\frac{E\left[p|p > 1 - \frac{D}{c-R}\right] \cdot \Pr\left(p > 1 - \frac{D}{c-R}\right) + E\left[p|\frac{d}{R} < p < 1 - \frac{d}{c-R}\right] \cdot \Pr\left(\frac{d}{R} < p < 1 - \frac{d}{c-R}\right)}{\Pr\left(p > 1 - \frac{D}{c-R}\right) + E\left[p|\frac{d}{R} < p < 1 - \frac{d}{c-R}\right] \cdot \Pr\left(\frac{d}{R} < p < 1 - \frac{d}{c-R}\right)}$$

where the higher delay cost is incorporated into the drugs that arrive in S.

The cost of delay decreases the threshold at which drugs are immediately approved: this leads to a simultaneous increase in quantity, as well as a decrease in quality. The quality and quantity of drugs delayed from $S-1$ is the same in period S as it was in period s.

This model predicts that, in high delay-cost periods, the regulator lowers the quality threshold necessary for approval. This both increases the number of drugs that are approved and decreases their average quality. Importantly, this model predicts that the quality of drugs approved in high delay-cost periods can be lower even though the quality of drug candidates *considered* during this period is the same (because the arrival rate of the new drugs, as well as potential holdovers from the prior period, is the same for high and low delay-cost periods). In essence, the quality of approved drugs is lower because the regulator rushes to meet a more salient deadline.

Relative to a world where the cost of delay is d in all periods, the presence of high delay-cost periods leads regulators to make more decisions immediately without acquiring additional information. This means that there is a mass of drugs of intermediate quality that are immediately approved when $t = S$, that would have been delayed had they arrived in period $t = s$. Because not all delayed drugs turn out to be safe, this means that there are dangerous drugs approved in high-cost periods that would have been more thoroughly investigated—and ultimately rejected—had delay costs been lower.

In the remainder of the paper, we provide empirical evidence consistent with the idea that natural calendar year benchmarks correspond to high delay-cost periods during which drug approval decisions appear to be rushed.

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