Internal Deadlines, Drug Approvals, and Safety Problems Online Appendix

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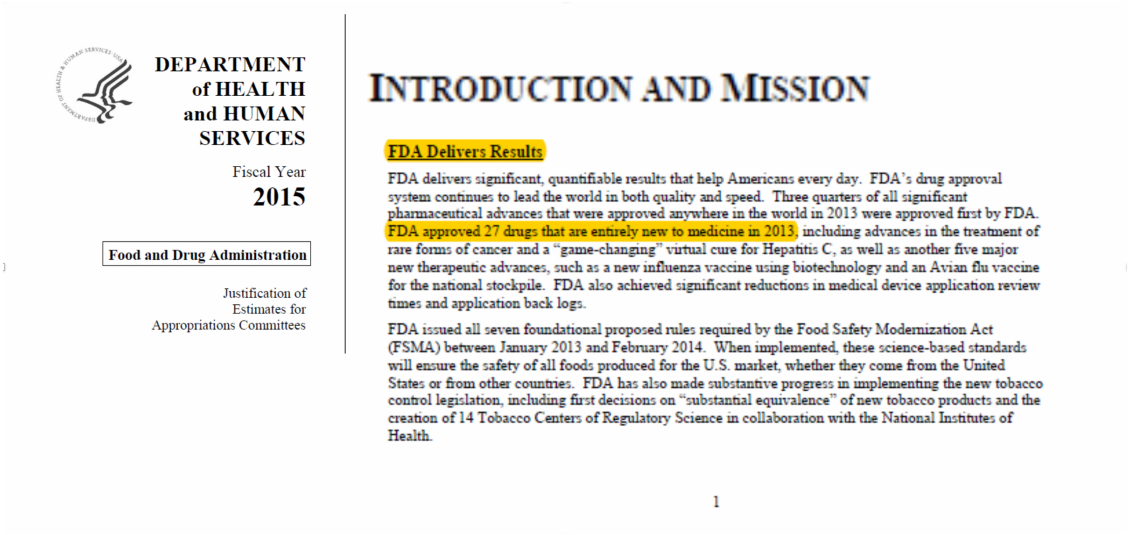
Appendix Exhibit 1



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

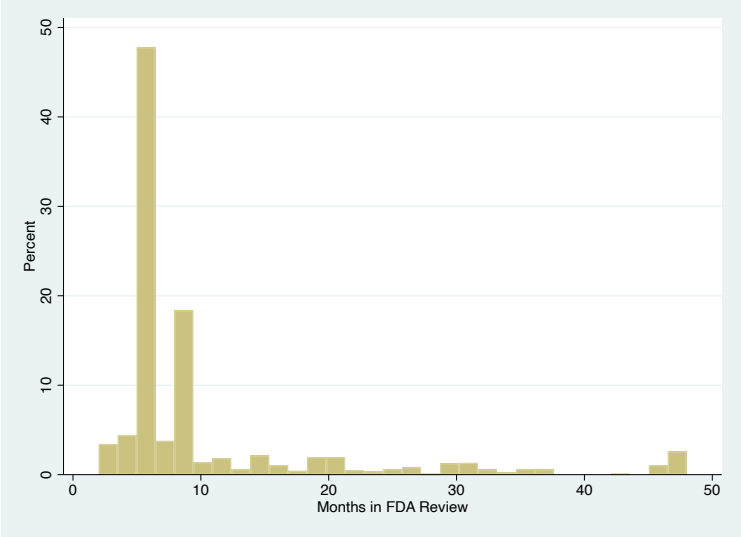
Panel A. Above is a link to a report by the then-Commissioner of the FDA (Scott Gottlieb) in December 2018 touting the record number of new drug approvals.

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

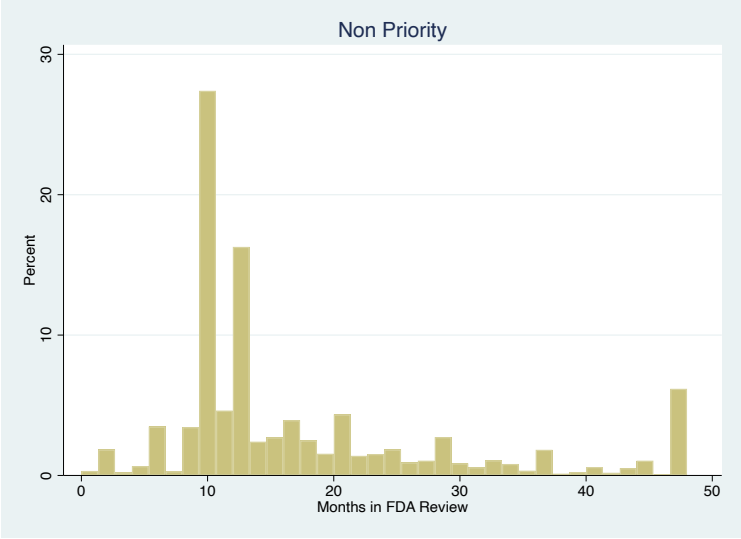


Table A1: Approvals in December and End of Month

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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