User Fees and 
FDA New Drug Review: 
Analysis and Policy Options

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FDA Symposium
August 24, 2006
PDUFA

Assume all here know, but…

(1) Per-application tax on sponsors, most proceeds to “buy” NDA reviewers

(2) Lots of other things in the legislation (FDAMA – “micromanagement,” conferences)

(3) Crucial mechanism: review time goals, or deadlines, a.k.a. “PDUFA clocks.”
Why Acceleration?

Lots of things have been happening

(1) Faster government (part management, part politics)
(2) More people
(3) Pressure for disease advocacy groups
(4) Changing culture at FDA? [Possibly; many here would know better than I would]
Empirical Study

Focus on review-specific deadlines. Use flexible and general statistical approach to address two questions:

**Q1:** Have PDUFA clocks changed FDA review behavior? Assess changes in behavioral review cycle before versus after deadline;

**Q2:** Have PDUFA clocks changed outcomes of FDA decision making? Assess whether changes in decision patterns have been associated with different policy outcomes.

**KEY:** need flexible deadline, so can observe post-deadline choices
Clocks by Statute

**PDUFA, 1992 (began 9/1992):** by 1997, review and act upon 90% of standard drugs in **12 months**, 90% of priority drugs in **6 months**.

**FDAMA, 1997 (began 10/1997):** by FY 1999, 30% of standard drugs in **10 months**, by FY 2002 90% of standard drugs in **10 months**; same as PDUFA for priority drugs.

**“PDUFA III,” 2002 (began 10/2002):** For standard and priority drugs, same deadline months as in FDAMA.
Method for Q1: Partition Review Time by Relevant Intervals

Modification of Cox proportional hazards model; can estimate several review cycles at once.
Semi-parametric Approval Hazard Ratio (AHR) estimates, by user-fee regime, non-priority NMEs

AHR_Cox

Hazard pre1993
PDUFA
FDAMA
PDUFA_CI_low
PDUFA_CI_high
FDAMA_CI_low
FDAMA_CI_high

month
Figure 2: Approval Hazard Ratios for Priority NMEs, before and after PDUFA

Month of Priority NME Review

AHRs before PDUFA
AHRs after PDUFA
Empirical Question 2: Compare “Outcome” Measures for Approvals before and after Deadline

Gather data on post-marketing regulatory events (PMREs) (withdrawals, black-box warnings, etc.)

Compare PMRE rates for drugs approved before versus after deadline.

Use nearest-neighbor matching techniques to balance samples.
Figure 3: Ratio of Increase in Post-Marketing Regulatory Event (PMRE) Rate, before versus after statutory deadline, Non-Priority NMEs

[bars are multipliers with 95% upper confidence interval shown]
### Table Z5:
Results from Nearest-Neighbor Matching Analyses

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<td>3.5973 (0.5791)</td>
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Conclusions

1. Still under revision; tentative.
2. Policy implications: Deadlines for regulatory decision need further scrutiny [FDA user-fee act up for reform in 2007].
3. Are there other ways of accelerating regulators?
4. Theoretically, need model of dynamic optimization in organizational or network context (might explain piling in penultimate period).
Modest Proposal

Why Not Harness User Fees for Drug Safety?

(1) Increase per-application fees by a tax, spend $ on RCTs and epidemiological data, plus FDA K investments for safety

(2) Would prob help FDA reputationally.

(3) Would help PhRMA, industry politically.

(4) If FDA/NIH conducts studies, less legal liability for firms (who can’t have “known ahead of time” about postmarket risks)

(5) Would increase funding for ‘post-market’ safety research, currently quite low.
Additional Slides
Questions

How to get at the effects of deadlines for regulatory review processes?

What is the impact of user-fee laws (micro: clocks) on FDA behavior?

What is the impact of clocks on postmarketing experience and safety of drugs?
PDUFA


(1) Per-application tax on sponsors, most proceeds to “buy” NDA reviewers

(2) Lots of other things in the legislation (FDAMA – “micromanagement,” conferences)

(3) CLOCKS – review time goals
More Information

“FDA Project” at

http://people.hmdc.harvard.edu/~dcarpent/fdaproyect.html

Professor Carpenter neither seeks nor accepts research funding or any other form of compensation from the FDA or from companies that sponsor product applications to the FDA. (Nor from patient advocacy groups, nor from Public Citizen.) This research supported by National Science Foundation (SES-0076452, SES-0351048), the Investigator Awards in Health Policy Program of the Robert Wood Johnson Foundation, and the RWJ Scholars in Health Policy postdoctoral program.
Roadmap

1. Discuss recent debates over drug approval and user fees
2. Discuss findings of statistical research re PDUFA
3. Discuss potential problems
4. Shamelessly sell my idea to fund postmarketing efficacy/safety studies through PDUFA augment.
Myth #1: Quicker Approval Necessarily Related to Safety Problems

DeAngelis, Rennie (JAMA Dec 2004): safety problems “unavoidable consequence” of acceleration of review.

There may indeed be a probabilistic relationship, but (1) that’s different from an “unavoidable consequence,” and (2) this requires investigation and is something we ought to know about.

Myth #2: Yesterday’s Approval is Necessarily Better than Today’s

Sam Kazman, others: If FDA announces approval of life-saving drug today, we should ask why it couldn’t have reached the market two years ago. [Paraphrase.]

Bad argument: (1) Part of development and review process is learning about optimal dosage, administration, utilization, prescription. The benefits as well as the risks are learned. (2) Cannot separate “benefits of a drug” from the value of learning through the development and regulatory process. (3) Statistical counterfactuals that backdate possible gains from drug (e.g., Wardell, Lasagna, others) are deeply flawed for this reason. Cannot validly use postapproval information to estimate what earlier-approval benefits would have looked like.
Focus on Analytic Question
[We Report, You Decide!]

How to best analyze variations in approval and development times?

What accounts for acceleration of FDA review of NMEs?
Problems in Previous Research

Reliance on linear statistical models
- Mary Olson
- Ernie Berndt/ Thomas Philipson et al

Linear regressions are bad: (1) atheoretical and ignore structure of data, (2) can’t retrieve parameters of interest, (3) miss important mean-variance dependencies

No clearly preferable “best” estimator for working on the problem; Carpenter and Ting (2005) working on this. Simultaneous equations with neuro-dynamic programming (aka “neural network” models).
Approach here

Focus on one specific mechanism of user-fee program, namely review-specific deadlines. Use flexible and general statistical approach to

(1) see whether it has changed FDA decision making and

(2) assess whether changes in decision patterns have been associated with different post-marketing outcomes.
Theory: Bureaucratic Learning and Regulatory Choice

Regulatory approval (e.g., FDA drug review) is a stopping problem

1. FDA guards reputation for protecting safety, sees approvals as irreversible

2. FDA has uncertainty over drug. Must decide, in real time, if and when apparent benefits outweigh apparent costs.
THE VALUE OF WAITING TO APPROVE

Delay is a way of getting more information about a risky (irreversible) decision.

FDA can recall a dangerous drug, but recall can’t undo the reputational damage from its mistake.

**Best Rule:** Approve drug when estimated danger is less than approval payoff AND value of waiting.

**BUT:** Value of delay not constant; it depends upon worth of information to be learned by waiting.
Basic Model

Regulator (R) learns about stochastic process that is both discrete (Poisson process) and continuous (Brownian motion).

R observes both processes, wishes to learn their underlying parameters: \( \mu \) (efficacy) and \( \lambda \) (danger)

Deadline is non-absolute: If R stops by deadline, “bonus” attached to terminal payoff. If R keeps going, loses bonus.
Regulator’s Observable and Problem

\[ X(t) = \mu_{ij} t + \sigma_{ij} w(t) - \sum_{k=1}^{D_t(\lambda_{ij})} Z_k \]

Objects of inference. But only \( X(t) \) observed.
Figure 1: Simulated First Passage of the Evidence Process through the Agency's Approval Barrier \( \eta(t) \)
Add Deadline (non-Absolute)

Want to model a situation where the incentives for approving in the next time interval change discontinuously according to the passing of a deadline.

Idea here: adopt deadline bonus, which disappears (= penalty) after deadline elapses.
Deadlines

Bayesian optimal stopping intensively studied, but almost always in context-free models:

(1) No deadlines
(2) No queues or networks of problem flow

Address (1): what happens to dynamic choice when a deadline is imposed?
Figure 2: Simulated First Passage of the Danger Process \( \gamma(\mu, \lambda, t) \) through the Agency's Approval Barrier \( \eta(t) \), with Penalty-Adjusted Barrier.

Deadline Bonus disappears at \( t = 84 \) periods.

First Passage at \( t = 80 \)

Posterior Variance \( S_t \) of Diffusion

Continuation Region (below barrier)

Stopping Region
Main Results

1. R’s behavior is highly non-continuous around the deadline.

2. R more prone to Type I error (stopping when shouldn’t have) when the stochastic process has a “jump” component.
   - 1st event may not have materialized
   - Underestimate in priors for rare events is non-linear (near-exponential)
Method for Q1:

Implement “augmented” Cox model that integrates density/hazard over months, within reviews

\( N \) is counting process (locally Poisson)

\( R \) is 1 if drug \( i \) is under review at time \( s \), 0 else

\[
PL(\beta) = \prod_{i=1}^{n} \prod_{t_i \geq 0} \prod_{s=0}^{t_m} \left\{ \frac{R_i(s) e^{X_i(s)\beta}}{\sum_{j} R_j(s) e^{X_j(s)\beta}} \right\} dN_i(s)
\]
Method for Q1:

Log-partial-likelihood is then

\[ l(\beta) = \sum_{i=1}^{n} \sum_{t_m=1}^{t_i} \left[ R_i(s)X_i(s)\beta - \ln \left( \sum_{j} R_j(s)e^{X_i(s)\beta} \right) \right] dN_i(s) \]

With score vector

\[ U(\beta) = \sum_{i=1}^{n} \sum_{t_m=1}^{t_i} \left[ X_i(s) - \bar{x}(\beta, s) \right] dN_i(s) \]

Add Γ-distributed frailty (unit mean, enters multiplicatively), shared by primary indication of NME
```r
> coxclock3 <- coxph(Surv(.t0, .t, .d) ~ stafcder + subyear + month1pdufa + month2pdufa + month3pdufa + month4pdufa + month5pdufa + month6pdufa + month7pdufa + month8pdufa + month9pdufa + month10pdufa + month11pdufa + month12pdufa + month13pdufa + month14pdufa + month15pdufa + month16pdufa + month17pdufa + month18pdufa + month19pdufa + month20pdufa + month21pdufa + month22pdufa + month23pdufa + month24pdufa + month7fdama + month8fdama + month9fdama + month10fdama + month11fdama + month12fdama + month13fdama + month14fdama + month15fdama + month16fdama + month17fdama + month18fdama + frailty(discode), data = approved.drugdata.st.20051108.subset.TVC, subset = priority == 0, na.action = na.exclude, eps = 0.0001, iter.max = 10, method = "efron")

> summary(coxclock3)

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Iterations: 8 outer, 18 Newton-Raphson
Degrees of freedom for terms= ... 
Variance of random effect= 0.0676   I-likelihood = -9696.3
Rsquare= 0.015   (max possible= 0.436 )
Likelihood ratio test= 518  on 83.7 df,  p=0
Wald test            = 354  on 83.7 df,  p=0

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Q1: Then use score or “Wald”-like tests to compare monthly rates

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<td>1.9e-003</td>
</tr>
<tr>
<td>month11fdama</td>
<td>-0.87136</td>
<td>0.46675</td>
<td>0.466074</td>
<td>3.49</td>
<td>1.0</td>
<td>6.2e-002</td>
</tr>
<tr>
<td>month12fdama</td>
<td>0.78953</td>
<td>0.62791</td>
<td>0.627265</td>
<td>1.58</td>
<td>1.0</td>
<td>2.1e-001</td>
</tr>
</tbody>
</table>
Table 1: Rates of Post-market Regulatory Events, before and after PDUFA deadline, for Priority Drugs

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval in 5th or 6th month, priority drug (pre-deadline)</td>
<td>3.8%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Approval in 7th or 8th month, priority drug (post-deadline)</td>
<td>16.3%</td>
<td>33.3%</td>
<td>37.9%</td>
<td></td>
</tr>
<tr>
<td>Black-box listing (Lasser et al)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety-based withdrawal, Canada</td>
<td>3.7%</td>
<td>1.1%</td>
<td>0.0%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Black-box warning (KUMC)</td>
<td>31.5%</td>
<td>33.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tests for Difference</td>
<td>Pearson $\chi^2 = 6.61$ [Pr = 0.010]</td>
<td>Pearson $\chi^2 = 0.3424$ [Pr = 0.558]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient population changes per year</td>
<td>0.027</td>
<td>0.000</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Tests for Difference</td>
<td>Regression $F = 1.16$ [Pr = 0.283]</td>
<td>Regression $F = 0.00$ [Pr = 0.994]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuations/year</td>
<td>0.041</td>
<td>0.000</td>
<td>0.013</td>
<td>0.026</td>
</tr>
<tr>
<td>Tests for Difference</td>
<td>Regression $F = 1.53$ [Pr = 0.219]</td>
<td>Regression $F = 0.12$ [Pr = 0.725]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 2: Rates of Post-market Regulatory Events, before and after PDUFA deadline, for Non-Priority Drugs

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval in 9th or 10th month [pre-deadline]</td>
<td>Approval in 11th or 12th month [post-deadline]</td>
<td>Approval in 11th or 12th month [pre-deadline]</td>
<td>Approval in 13th or 14th month [post-deadline]</td>
<td>Approval in 13th or 14th month [pre-deadline]</td>
<td>Approval in 13th or 14th month [post-deadline]</td>
<td></td>
</tr>
<tr>
<td>Black-box listing (Lasser et al)</td>
<td>0.0%</td>
<td>0.0%</td>
<td>4.2%</td>
<td>0.0%</td>
<td>1.5%</td>
<td>3.1%</td>
</tr>
<tr>
<td>F-test in regression: 1.24 [Pr &lt; 0.247]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson $\chi^2 = 0.5567$ [Pr = 0.456]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-test in regression: 0.46 [Pr &lt; 0.497]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black-box warning (KUMC)</td>
<td>17.4%</td>
<td>10.0%</td>
<td>16.7%</td>
<td>46.2%</td>
<td>18.2%</td>
<td>15.0%</td>
</tr>
<tr>
<td>F-test in regression: 1.89 [Pr &lt; 0.170]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson $\chi^2 = 3.7176$ [Pr = 0.051]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F-test in regression: 0.47 [Pr &lt; 0.722]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety-based withdrawal, Canadian market</td>
<td>8.6%</td>
<td>1.4%</td>
<td>11.5%</td>
<td>0.9%</td>
<td>0.0%</td>
<td>2.1%*</td>
</tr>
<tr>
<td>F-test in regression: 0.73 [Pr &lt; 0.392]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson $\chi^2 = 8.5834$ [Pr = 0.003]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>F-test in regression: 7.40 [Pr &lt; 0.007]</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>F-test in regression: 0.23 [Pr &gt; 0.999]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient population changes per year</td>
<td>0.011</td>
<td>0.000</td>
<td>0.016</td>
<td>0.000</td>
<td>0.005</td>
<td>0.006</td>
</tr>
<tr>
<td>F-test in regression: 1.26 [Pr &lt; 0.2615]</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>F-test in regression: 3.84 [Pr &lt; 0.0503]</td>
<td></td>
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</tr>
<tr>
<td>F-test in regression: 0.00 [Pr &lt; 0.9489]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Product discontinuations per year</td>
<td>0.095</td>
<td>0.000</td>
<td>0.080</td>
<td>0.041</td>
<td>0.030</td>
<td>0.024</td>
</tr>
<tr>
<td>F-test in regression: 41.84 [Pr &lt; 0.0001]</td>
<td></td>
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<tr>
<td>F-test in regression: 2.89 [Pr &lt; 0.091]</td>
<td></td>
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</tr>
<tr>
<td>F-test in regression: 0.33 [Pr &lt; 0.565]</td>
<td></td>
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</tr>
</tbody>
</table>

* Pearson chi-squared statistic not calculable; too few data points in relevant categories.

# Because so few drugs were approved in 13-14 month interval before 1993, we extend the after deadline period to 18 months.
Linear FE Regressions

\[ \text{EVENTRATE}_i = \alpha + \beta(DIZ_i) + \gamma(FIRM_i) \]
\[ + \delta_1 \text{Approval0910} \]
\[ + \delta_2 \text{Approval 1112} \]
\[ + \delta_3 \text{Approval 1314} \]
\[ + \delta_4 \text{Approval 1112-PDUFA} \]
\[ + \delta_5 \text{Approval 1314-PDUFA} \]
\[ + \delta_6 \text{Approval0910-FDAMA} \]
\[ + \delta_7 \text{Approval1112-FDAMA} + \text{othervars} + \text{error} \]
Figure 3
Differentials in Regulatory Event Rates by Deadline Status

<table>
<thead>
<tr>
<th>Event Rate Differential</th>
<th>as Multiple of Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference from 11th- and 12th-month approvals (PDUFA) to 13th- and 14th-month approvals (PDUFA)</td>
<td>7</td>
</tr>
<tr>
<td>Difference from 11th- and 12th-month approvals (PDUFA) to 11th- and 12th-month approvals (FDAMA)</td>
<td>6</td>
</tr>
<tr>
<td>Difference from 11th- and 12th-month approvals (PDUFA) to 11th- and 12th-month approvals (pre-PDUFA)</td>
<td>5</td>
</tr>
<tr>
<td>Difference between 9th- and 10th-month approvals (FDAMA) and 11th- and 12th-month approvals (FDAMA)</td>
<td>4</td>
</tr>
</tbody>
</table>

Legend:
- Basler
- Canadian withdrawal
- Patient pop chg per yr
- Discontinuation per yr
Global Withdrawals

Score “1” if withdrawn for safety reasons in at least one country (mean = 0.013). Shift is rate for two months after deadline to rate for two months before.

PDUFA shift/mean = 2.85; \( F = 0.58 \) (0.44) [FE]
3.17 [RE]; \( F = 0.95 \) (0.33)

FDAMA shift/mean = 8.06; \( F = 2.78 \) (0.09) [FE]
8.80 [RE]; \( F = 4.58 \) (0.03)
Possible Policy Concerns

1. Do artificial deadlines induce suboptimal decisions? (Probably inconsistent with optimal stopping behavior, but this needs to be tested.)

2. Are there ways other than deadlines to accelerate expected review times?

3. What about drugs “orphaned” by the passage of deadline?
Extra Slides, just in case you asked

\[
\sup E_{x,t} e^{-\delta(t_{app})} \left\{ A - E_{\hat{\mu}, \hat{\lambda}, t} \int_t^\infty e^{-\delta(y-t)} \left[ \mu^*(s, \omega) + \lambda^*(s, \omega) \right] dy \right\} \\
= E e^{-\delta(t_{app})} \left\{ A - \delta^{-1} \left( \mu^*[t_{app}, \omega] + \lambda^*[t_{app}, \omega] \right) \right\}
\]
Figure 1: Center for Drug Evaluation and Research (CDER) Staffing Levels, 1980-1998

[Source: FDA Annual Reports, Statistical History]
Figure 2A: Actual Decline in NME Approval Times, 1980-1998
[approval times averaged by year of submission]
[Source: FDA Annual Reports, Authors’ Data]
Figure 2B: Average Approval Time for NMEs by year of submission with CDER staffing assumed constant at 1980 level (n=1,119).

[Source: FDA Annual Reports, Authors' Data]
EXHIBIT 2
Marginal Effects Of FDA Staff, Advocates’ Wealth, And Media Coverage On New Molecular Entity (NME) Approval Times

<table>
<thead>
<tr>
<th></th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lognormal baseline minus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effect of CDER staff</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lognormal baseline minus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effect of advocates’ wealth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lognormal baseline minus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effect of media coverage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lognormal baseline</td>
<td></td>
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</tr>
<tr>
<td>(no controls)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gamma baseline minus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>effect of CDER staff</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gamma baseline minus</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>effect of advocates’ wealth</td>
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<tr>
<td>Gamma baseline minus</td>
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<td></td>
<td></td>
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<tr>
<td>effect of media coverage</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gamma baseline</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(no controls)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Expected FDA approval time (months)

**SOURCE:** Author’s maximum likelihood duration analyses of Food and Drug Administration (FDA) approval times.

**NOTES:** Estimates from lognormal and gamma duration models. Effect of one-standard-deviation increase in each item depicted. See text for details. CDER is Center for Drug Evaluation and Research, FDA.
Necessary Extensions

1. No control for quality/safety [working on this]
2. Crucial covariates missing: order of entry
3. Would like more general model, then maybe structural estimation
4. All observational → No attempt at instrumental variables here
My Previous Research


1. Resources, before and after PDUFA
   a. Resources rise, and apptimes decline, in mid- to late-1980s
   b. Acceleration among drugs that were not targeted with clocks (generics), but still reviewed by CDER.

2. Patient advocacy and news coverage

3. Acceleration not concentrated among politically powerful, larger firms
Not Everyone Agrees

Mary Olson (Yale): Buys everything else, but points to PDUFA incentives.

My latest estimates: Acceleration is mix of resources and incentives ("clock")

My Q: Why would incentives matter if resources didn’t?
<table>
<thead>
<tr>
<th></th>
<th>Canadian withdrawal</th>
<th>Black-box warning (Lasser)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean of Regulatory Event Variable</td>
<td>0.0197</td>
<td>0.0526</td>
</tr>
</tbody>
</table>
| 11\textsuperscript{th} and 12\textsuperscript{th} month, PDUFA versus 13\textsuperscript{th} and 14\textsuperscript{th} month, PDUFA | Diff = 0.135  
As multiple of mean: 6.87  
F: 3.72  
Pr > F: 0.0540 | Diff = 0.102  
As multiple of mean: 1.95  
F: 6.77  
Pr > F: 0.0094 |
| 11\textsuperscript{th} and 12\textsuperscript{th} month, PDUFA versus 11\textsuperscript{th} and 12\textsuperscript{th} month, FDAMA | Diff = 0.112  
As multiple of mean: 5.67  
F: 8.80  
Pr > F: 0.0031 | Diff = 0.233  
As multiple of mean: 4.43  
F: 2.12  
Pr > F: 0.1492 |
| 11\textsuperscript{th} and 12\textsuperscript{th} month, PDUFA versus 11\textsuperscript{th} and 12\textsuperscript{th} month, pre-1993 | Diff = 0.058  
As multiple of mean: 2.92  
F: 9.55  
Pr > F: 0.0020 | Diff = 0.144  
As multiple of mean: 2.75  
F: 1.58  
Pr > F: 0.2086 |
| 9\textsuperscript{th} and 10\textsuperscript{th} month, FDAMA versus 11\textsuperscript{th} and 12\textsuperscript{th} month, FDAMA | Diff = 0.036  
As multiple of mean: 1.85  
F: 0.81  
Pr > F: 0.3686 | Diff = 0.062  
As multiple of mean: 1.18  
F: 0.29  
Pr > F: 0.5898 |
<p>| NMEs                     | 1,712               | 1,712                     |
| Indicator variables for primary indication | 201                 | 201                       |
| Fixed effects for firms   | Yes                 | Yes                       |</p>
<table>
<thead>
<tr>
<th>Mean of Regulatory Event Variable</th>
<th>Patient population changes per marketing year</th>
<th>Product discont. per marketing year</th>
</tr>
</thead>
</table>
| **11th and 12th month,** PDUFA versus 13th and 14th month, PDUFA | Diff = 0.020  
As multiple of mean: 2.48  
F: 4.29  
Pr > F: 0.0387 | Diff = 0.033  
As multiple of mean: 1.01  
F: 2.44  
Pr > F: 0.1188 |
| **11th and 12th month,** PDUFA versus 11th and 12th month, FDAMA | Diff = 0.035  
As multiple of mean: 4.48  
F: 6.97  
Pr > F: 0.0084 | Diff = 0.170  
As multiple of mean: 5.13  
F: 31.04  
Pr > F: 0.0000 |
| **11th and 12th month,** PDUFA versus 11th and 12th month, pre-1993 | Diff = 0.006  
As multiple of mean: 0.80  
F: 0.52  
Pr > F: 0.4691 | Diff = 0.061  
As multiple of mean: 1.85  
F: 10.31  
Pr > F: 0.0014 |
| **9th and 10th month,** FDAMA versus 11th and 12th month, FDAMA | Diff = 0.024  
As multiple of mean: 3.03  
F: 4.04  
Pr > F: 0.0447 | Diff = 0.179  
As multiple of mean: 5.42  
F: 42.58  
Pr > F: 0.0000 |
<p>| NMEs | 1,244 | 1,244 |
| Indicator variables for primary indication | 185 | 185 |
| Fixed effects for firms | Yes | Yes |</p>
<table>
<thead>
<tr>
<th></th>
<th>Mfg revisions per market year</th>
<th>Label revisions per market year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.1330</td>
<td>0.2251</td>
</tr>
</tbody>
</table>
| **11\textsuperscript{th} and 12\textsuperscript{th} month, PDUFA versus 13\textsuperscript{th} and 14\textsuperscript{th} month, PDUFA** | Diff = 0.018  
As multiple of mean: 1.39  
$F$: 8.13  
Pr $> F$: 0.0044 | Diff = 0.206  
As multiple of mean: 0.92  
$F$: 4.36  
Pr $> F$: 0.0371 |
| **11\textsuperscript{th} and 12\textsuperscript{th} month, PDUFA versus 11\textsuperscript{th} and 12\textsuperscript{th} month, FDAMA** | Diff = 0.363  
As multiple of mean: 2.72  
$F$: 15.54  
Pr $> F$: 0.0001 | Diff = -0.152  
As multiple of mean: -0.68  
$F$: 1.18  
Pr $> F$: 0.2783 |
| **11\textsuperscript{th} and 12\textsuperscript{th} month, PDUFA versus 11\textsuperscript{th} and 12\textsuperscript{th} month, pre-1993** | Diff = 0.266  
As multiple of mean: 2.00  
$F$: 19.67  
Pr $> F$: 0.0000 | Diff = 0.030  
As multiple of mean: 0.13  
$F$: 0.08  
Pr $> F$: 0.7733 |
| **9\textsuperscript{th} and 10\textsuperscript{th} month, FDAMA versus 11\textsuperscript{th} and 12\textsuperscript{th} month, FDAMA** | Diff = 0.003  
As multiple of mean: 0.02  
$F$: 0.00  
Pr $> F$: 0.9712 | Diff = -0.198  
As multiple of mean: -0.88  
$F$: 2.52  
Pr $> F$: 0.1129 |
| **NMEs**                      | 1,244                         | 1,244                           |
| **Indicator variables for primary indication** | 185                           | 185                             |

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