Groups, the Media, Agency Waiting Costs, and FDA Drug Approval

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Why does the FDA approve some drugs more quickly than others? I model drug review as a process of bureaucratic learning. Political influence occurs when politicians, firms, disease-specific organizations, and the media shift the FDA's case-specific *waiting costs*. I test the predictions of this theory using duration analyses of review times for 450 drugs reviewed from 1977 to 2000. In contrast to recent research on political control of the bureaucracy, drug approval times appear insensitive to shifts in the partisanship or ideology of congressional majorities, oversight committees, and presidents. Controlling for numerous clinical factors, FDA review times are decreasing in (1) the wealth of the richest organization representing the disease treated by the drug, (2) media coverage given to this disease, and (3) a nonlinear function of the number of groups representing this disease. Political influence over drug approval operates primarily through "salience signals" transmitted by groups and the media.

Why do agencies make some decisions more quickly than others? This is a central issue of bureaucratic government in the United States. Americans usually complain less about the choices that bureaucrats make than they do about the *delay* with which these choices are made. To this question the literature in political science says little: what happens when *time itself* is the variable of bureaucratic choice?

It is the timing of agency decisions, more than their content, which fuels some of the central controversies in contemporary bureaucratic politics—including "Year 2000" problems, military contracting, construction permits, license approval, prosecuting or apprehending criminal suspects, even returning tax refunds. Yet the issue of timing has nowhere figured more prominently than in debates over the federal government's approval of new pharmaceutical products. This policy, delegated to the U. S. Food and Drug Administration (FDA), has been the subject of two major laws during the last ten years. Yet much of the debate over drug approval concerns not *whether* the FDA rejects or approves too many new drugs, but *how long* it takes for safe and efficacious drugs to get approved.

There is immense variance in review times across drugs. From 1993 to 1995, the FDA approved sixty-seven new chemical entities (NCEs), but the drug *Flumadine* (marketed by Forest Labs) spent eighty-two months in the drug review process, whereas *Orlaam* (BioDevelopment Corp.) was approved in less than a month. Herein lies a central puzzle of U.S. pharmaceutical regulation: why does an agency that approves some drugs very quickly take so much time with others?

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Many standard explanations for agency decisions fail to account for this variation. Drugs are reviewed under the same statutes—the 1938 Food Drug and Cosmetic Act as amended by the Kefauver-Harris Amendments of 1962—by the same agency, and under identical administrative procedures. All of these decisions are made at FDA headquarters, ruling out regionally-based explanations of the variance (Whitford 2000; Gordon 1999). Moreover, FDA review occurs only after pharmaceutical companies have completed three stages of clinical trials on the drug. The requirement that firms provide all information to the FDA drastically reduces the agency's information costs and reduces the variance of product uncertainty in drug review. Agency design, administrative procedures, or informational barriers will, by themselves, have difficulty explaining the variance in FDA review times.[1]

This article analyzes drug approval by focusing on its decision structure. At its core, drug approval is an optimal stopping problem. The agency receives a drug submission over which it has uncertainty about some key characteristics, mainly the safety and efficacy of the drug. The agency will learn about the drug over the course of a review as a way of reducing this uncertainty, stopping the learning process to approve the drug if and when the benefits of waiting are exceeded by the costs of further delay. This has similarities with criminal and civil prosecutions (Gordon 1999), permit granting (Whitford 1999), and license granting and renewal (Spence 1999). For problems of this sort, political influence over the agency occurs through shifts in the *waiting cost*. When political "principals" or interested groups influence the FDA's cost of delay, they can speed up (or slow down) FDA approval.

A central claim of this article is that *waiting costs are case-specific*, or drug-specific. For this reason, political influence in FDA drug approval occurs less through ideological and partisan shifts in the agency's oversight institutions (the presidency, Congress and its committees; Moe 1985; Wood and Waterman 1992), and more through organized interests (e.g., Vogel 1989; Scholz, Twombly, and Headrick 1991; Brehm and Gates 1997, Chapters 9 and 10) and the media. When disease-specific advocates and media organizations give greater publicity to a disease and its sufferers, they boost the political salience of that disease (and its sufferers) and render it more costly for the FDA to delay approval for beneficial therapies.

[1]Agency design and administrative procedures should not, however, be ignored. The structure of the FDA and the administrative procedures of review doubtless influence review times. The point here is that, within any class of drugs and within any given year, review times vary widely, and a sound explanation cannot be based on these factors alone.

Relationship to previous studies. My argument builds upon and differs from previous research on FDA drug approvals. Dranove and Meltzer (1994), in one of the first multivariate analyses of FDA review times, find that more "important" drugs reach the market sooner. Olson (1997) finds that firms with more applications and greater research intensity receive shorter drug approval times and suggests that FDA regulators see these variables as proxies for higher-quality submissions. I extend these analyses in two ways. First, I offer a theoretical framework for assessing when and why the FDA might consider some drugs more important than others and why importance translates into shorter review times. Second, I focus squarely on citizen- and media-based determinants of salience in FDA regulation. This is crucial because several scholars (Vogel 1989, 1990; Burkholz 1992; Epstein 1996) have argued that organized disease advocates and the media have shaped FDA drug review. This claim has not, however, been subjected to a quantitative test.

Drug Approval as a Stopping Problem

At its core, product approval presents the regulator with a learning problem. The regulator must study a new product application (with accompanying tests and data) and decide when the apparent benefits of the drug outweigh the costs or risks associated with its use. These costs and benefits are politically determined.

Reputation and the Value of Waiting to Approve

Like other agencies, the FDA protects its reputation, specifically its reputation as guarantor of the public safety in the pharmaceutical market. Bureaucratic reputations are valuable political assets—they can be used to generate public support, to achieve delegated authority and discretion from politicians, to protect the agency from political attack, and to recruit and retain valued employees (Carpenter 2001). To protect its reputation, the FDA aims to minimize the danger of adverse drug reactions from approved products (Quirk 1979; Heimann 1997).

To minimize this danger is not easy. For the danger of any given drug, like the failure propensity of a space shuttle (Heimann 1992), can not be known with certainty in advance. In the case of product approval, the agency must learn about product danger by reviewing experimental evidence. For this reason, information is at a premium in product approval, and because learning more about the drug requires additional studies and additional

time to review them, *there is always a value to waiting.* Waiting is a way of "buying" more certainty. Yet although waiting to approve always has *some* value, there is not always a *net benefit* to waiting. In other words, in many cases it is *not* optimal to wait forever. As with most inference problems in politics, the marginal return to more information is decreasing.

Groups, the Media and Costly Delay: The Approval Payoff as a Waiting Cost

There is another reason why waiting is not always optimal. Put simply, waiting is politically costly. Patients want a drug for their disease, and firms that profit from drug sales want entry into potentially lucrative markets. To delay the approval of a drug is to impose costs upon these interests, and when these interests are organized or well publicized, they can make it costly for the agency to delay. The case of AIDS offers a lucid example. When ACT-UP protesters, dismayed that the FDA might delay approval of lifesaving therapies, demonstrated at agency headquarters in 1988, they embarrassed the agency and prompted a sharp change in policy on AIDS drugs.

An Optimal Stopping Model of Drug Approval

Using the logic laid out above, I now advance an optimal stopping model of the FDA approval process. Let all drugs be indexed by i, diseases by j, firms by k. Assume an exogenous industry production process, in which drugs can treat one disease and one disease only. All drugs in the model are characterized by two parameters. First, let γ_{ij} $(0 < \gamma_{ij} \leq 1)$ be the *curing probability* of the drug (which is the fraction of people with disease j that drug i will cure). I assume that γ_{ij} is fixed and known with certainty throughout the drug review. Second, let μ_i be the *danger* of the drug, which can be thought of as the expected number of people that will be harmed or killed by the drug over a given interval of time. In other words, μ_i is the *rate* of harming consumers. The greater the danger of the drug, the more its approval will harm the agency's reputation for protecting public safety.[2]

[2]The agency does regulate drugs based upon their safety and their efficacy in this model, but for simplicity, I assume that only danger is subject to uncertainty. The model is easily adapted to the case where γ_{ij} is learned as well, but the dynamics become quite complex. I assume that a drug's danger is independent of its curing power, which implies $\text{cov}(\mu_i, \gamma_i) = 0$. If danger and curing power are correlated, then the learning process is easier because information about curing provides information about danger, and vice versa.

Learning about Danger

I assume that the evolution of observed harm in regulatory review follows a Wiener process $X_{it} = X(t)$, a linear function of the underlying danger of the drug (μ) plus a random component, as follows,

$$X(t) = \mu t + \sigma z(t) \tag{1}$$

where μ and σ are constants and $\sigma > 0$, and where $z(t)$ is a standard normal variable with mean zero and variance t. A more "dangerous" drug—one with higher μ—yields more harm, but harm is also affected by the random term $z(t)$. A higher σ yields a more volatile review—namely a series of "data" from which the agency finds it harder to learn what μ is.

Observed harm is therefore a Markov process, and the agency learns about μ in a simple Bayesian fashion based upon the stochastic history of $X(t)$. For any drug review of length t and accumulated harm $X(t) = x$,[3] Bayesian estimates of μ are

$$\text{Posterior Mean} \equiv \hat{\mu} = \frac{m/s + x/\sigma^2}{1/s + t/\sigma^2};$$

$$\text{Posterior Variance} \equiv S(t) = \frac{1}{1/s + t/\sigma^2} \tag{2}$$

Danger and the Protection-Provision Tradeoff

The approval of a truly dangerous drug will carry reputational costs for the agency that cannot be regained. Although real-world agencies have the option to recall a bad product (or, more properly, to induce a recall by producers), the agency has no such option in the model here. Once the drug has done sufficient harm that it must be recalled, the agency cannot recover its reputational losses by recalling the drug. Everyone will know that the agency has made a "bad" decision. In this respect the decision to approve a drug is reputationally irreversible.

Yet the "costs" of approving dangerous drugs depend in part upon how agency decisionmakers view the tradeoff between satisfying patient demand and protecting consumer safety. More liberal legislators and executives have traditionally pressed the FDA not to approve unsafe drugs, deferring to the concerns of consumer safety advocates such as Ralph Nader. More recently, conservative politicians—responding in part to the concerns

[3]See Jovanovic (1979) and, originally, Miroschnichenko (1975) for a similar set-up. Letting $X(t)$ start arbitrarily at 0, then it is normally distributed with mean μt and variance $\sigma^2 t$. I assume that σ is the same across drugs but that μ differs across them, according to a normal distribution with mean m and variance s.

of a more powerful pharmaceutical industry, in part to patient advocacy groups—have pressed the FDA to accelerate its drug approvals, even suggesting private third-party review as a way of speeding up the drug approval process. Given a long line of research showing bureaucratic responsiveness to elected politicians (e.g., Wood and Waterman 1991), we should expect the agency's relative preference for consumer protection versus drug provision to be politically determined, at least in part.

To capture this effect, let α $(0 < \alpha < \infty)$ represent the *protection-provision tradeoff*, or the agency's preferred level of tradeoff between protecting consumer safety and satisfying political demand. A high level of α implies a danger-averse agency $(\alpha > 1)$,[4] one that places high weight on μ relative to the demands of those who wish the drug to be approved. A low level of α represents a consistent agency predilection to emphasize political demand for the drug over the goal of consumer safety protection $(\alpha < 1)$. This parameter is then

α = Agency's Relative Weight on Consumer Protection versus Quick Approval
= f(partisanship, ideology of Congress, president)

Upon the approval of the drug, then, the agency "pays" the parameter $\alpha\mu$, where μ is learned only through review.

The Political Demand for Drugs and the Approval Payoff

One way for the FDA to protect its reputation would be to review drugs forever (or reject them all). Yet delaying or rejecting a drug is also costly. Bureaucracies generally wish to avoid criticism, particularly criticism that is visible or amplified (Wilson 1989, 197; or see the "external signals" theory in Olson 1997). The benefit of approval is that constituencies who are potentially or actually dissatisfied with the agency's delay (e.g., patients who need the drug, firms wishing to market it) are mollified. The agency's *approval payoff* may be defined as:

> For any drug i, which treats disease j and is submitted by firm k, the payoff from approving the drug (denoted by A) is equivalent to the sum of all individuals with disease j who have no available pharmaceutical alternatives and whom drug i would cure, weighted by their relative political organization and a firm "clout value."

[4]The agency in the model here is always danger-averse $(\alpha > 0)$, but is assumed risk-neutral. That is, it is indifferent to relative gambles among drugs, but always prefers safer drugs to more dangerous ones, ceteris paribus.

A drug's approval payoff may be interpreted as the opportunity cost of delay. I assume that A is strictly positive and is a combinatorial and strictly decreasing function of the number of drugs that have already been approved for disease j,[5] as follows

$$A = (1+\lambda_k)\psi_j \gamma_{Nj} L_j \prod_{i=0}^{N_j - 1} (1-\gamma_{ij})$$

$$= (1+\lambda_k)\left[f(M_j + \mathbf{W}_j)\right]\gamma_{Nj} L_j \prod_{i=0}^{N_j - 1} (1-\gamma_{ij}) \tag{3}$$

where L_j is disease j's *prevalence*, or the number of persons with disease j and N_j is the number of marketed drugs that already treat disease j;

$\psi_j = f(M_j + \mathbf{W}_j)$ is the *political multiplier* of disease j, a positive parameter. We can interpret ψ_j as the expected number of citizens, for every citizen afflicted by disease j, who will apply pressure upon the agency or the politicians governing it;

M_j is the media coverage given to disease j where $\partial f / \partial M_j > 0$ (see discussion below), and $\mathbf{W}_j$ is a vector of characteristics relating to the organization of disease sufferers and advocates for disease j (variable relationships discussed below);

λ_k is the political clout of the submitting firm, also strictly positive.

Consumers and Patient Organization

The *political* demand for drug *approvals* is only loosely associated with the economic demand for drugs. Because most drugs are developed for specific diseases, the incidence or prevalence of the disease—generally, the size of affected population—is an important component of political demand. Yet drugs for diseases with greater prevalence do not always receive more favorable treatment by the FDA. Some diseases are more severe than others, and some disease communities are better organized than others. In particular, several scholars have documented the influence of organized disease advocates over FDA behavior (e.g., Epstein 1996; Vogel 1989, 1990).

[5]An implicit assumption here is that the *political* demand for drug approvals is relatively price insensitive. While individuals as consumers may care about price, *individuals as citizens* satisfice with respect to the agency. The reason, I suggest, is that citizens have "traceability" constraints (Arnold 1990). They do not blame the FDA for the high price of drugs—even if it would be apparent upon reflection that the FDA regulatory process increases pharmaceutical prices. If the price of a drug is too high, or if citizens are weakly satisfied with a drug they are taking, they blame not the agency, but the producers.

I focus initially on the organizational size of the disease community. First, one might expect that the FDA will find it harder to wait when the sufferers of a given medical condition are better organized or better funded. The greater the number of patient and provider groups representing a disease, and the better funded these groups (especially peak associations), the higher the FDA's waiting costs in reviewing drugs for this disease.

The link between resource wealth and political influence is similar. Net of the number of groups representing a disease, then the wealthier these groups, the greater their political influence. This is particularly so when one large group or umbrella association has a large budget. Let $W_j^{\#}$ be the number of groups representing a disease, and let $W_j^{\$}$ be the resource wealth of disease advocates. Then the relationships among organizational characteristics and the political multiplier can be stated as follows.

Disease-Organization Linearity Axiom:

$$\partial\psi_j/\partial W_j^{\#} > 0, \text{ hence } \partial A/\partial W_j^{\#} > 0.$$

Disease-Organization Wealth Axiom:

$$\partial\psi_j/\partial W_j^{\$} > 0, \text{ hence } \partial A/\partial W_j^{\$} > 0.$$

Media

Scholars of news coverage have focused upon how media organizations determine "newsworthiness" (Cook 1999; Sparrow 1999). Diseases with greater severity and prevalence will usually be more newsworthy, but other factors, including reporters', editors', and producers' own preferences will also come into play.

The media are an independent agenda-setting force. They are the "privileged means of communication" and function as agenda-setting gatekeepers between politicians and the public (Baumgartner and Jones 1993, 107). When media organizations allocate substantial coverage to a disease, then drugs treating this disease will receive more attention from the public, interested groups, and politicians. As a result, any criticism of FDA delay will be amplified, and the costs of waiting to approve these drugs will rise. For FDA reviewers, media coverage may operate indirectly by shaping their general sense of which diseases carry greater public salience. Hence diseases without strong group organization such as meningitis, pancreatic cancer, or even erectile dysfunction can have heightened salience due to enhanced media attention. The case of AIDS is instructive. As Burkholz relates, "Only after the AIDS community had roared, screamed, and bullied the subject onto the front pages and the six o'clock news did the FDA begin to stir itself into a search for a better way to approve certain drugs" (1994, 113). In other words, media coverage was a *necessary* step in getting the FDA to prioritize AIDS drugs. This relationship generates a third axiom.

Media Coverage Axiom: $\partial\psi_j/\partial M_j > 0$, hence $\partial A/\partial M_j > 0$.

Firms

The benefits of drug approval for the agency are also a function of the power of the firm submitting the drug. With billion-dollar profits and locations in politically powerful states such as California, New Jersey, Illinois, Pennsylvania, and Michigan, pharmaceutical firms have become powerful political players in the last three decades. Yet the pharmaceutical industry, like many others, is characterized by inequality—small biotech firms coexist with global conglomerates like Merck and Pfizer. While firm political strategies are not the primary concern here, firm attributes undoubtedly sway the FDA's decision making in drug approval cases (e.g., Olson 1997).

Incumbent Drugs and Order-of-Entry Effects

Because political demand is a function primarily of those patients *without* therapeutic alternatives, the payoff to approval is not a simple function of the curing power γ_i of the drug submitted. The reason is that drugs may already exist to treat disease *j*. If previous drugs have been approved for disease *j*, then the approval payoff is lower than it would be in the absence of existing alternatives. Even in cases where drugs improve measurably over time, we should expect order-of-entry effects: the earlier a drug stands in the "pipeline" of all drugs for a given disease, the quicker will be its approval. (A formal model of early-entry effects appears in Carpenter 2000.)

Order-of-entry should affect not simply drug approval itself, but also the way in which other disease-based variables affect approval times (see Hypothesis 6, stated below). If a drug is the first to treat a medical condition, this advantage may be heightened if the sufferers of the condition are politically organized. The tenth drug to treat a disease, moreover, may receive less emphasis, but if the disease it treats is well represented, its order of entry disadvantages may be dampened. A formal example of these interactions is provided in the appendix (Proposition A-1); I provide a more rigorous treatment elsewhere.

The Agency's Optimal Policy

The agency's problem is the optimal stopping of the process $\alpha\hat{\mu}_t$ as described by (2), consistent with the following objective.

$$\max E\ e^{-\delta(t_{app})}\left\{A - E_{\hat{\mu},t}\int_t^{\infty} e^{-\delta(y-t)}\alpha\mu^*(y,\omega)dy\right\}$$
$$= Ee^{-\delta(t_{app})}\left\{A - \delta^{-1}\alpha\mu^*\left[t_{app},\omega\right]\right\} \quad (4)$$

where δ is the discount factor, t_{app} is a given approval time, $E_{\hat{\mu},t}$ is the expectation operator conditioned on $\hat{\mu}$ and t, μ^* is the agency's estimate of danger at the optimal stopping time, ω is an event in the probability space Ω, and y is a variable of integration.

The agency's solution to the approval problem is a first-passage time policy. The agency divides the space of possible points into two regions—a *waiting region* where observed values of danger ($\hat{\mu}$) suggest continued delay, and an *approval region* where observed values of $\hat{\mu}$ suggest stopping of the review and approval of the drug. The optimal policy can be represented by an approval barrier that uniquely separates these two regions. The agency optimally approves the drug when the stochastic process that represents the agency's best (Bayesian) estimate of danger passes *for the first time* through this barrier, from the waiting region (above) into the approval region (below).

Proposition 1: The optimal barrier is

$$\eta^*(t) = \delta A - \frac{S(t)^2}{2\sigma^2}F_{\hat{\mu}\hat{\mu}}\left[\eta(t),t\right] \quad (5)$$

Proof: All proofs are in the appendix.

Hypotheses

From equation (5) the following result, necessary for comparative statics, ensues.

Proposition 2: The expected time to approval is decreasing in the approval payoff A and increasing the protection-provision tradeoff α.

Proof: See Carpenter (2000) or contact author.

Given Proposition 2 and the specification of the approval payoff earlier, we can pose the following hypotheses.

H1: If α is an increasing function of the liberal ideology of the agency's overseers, then expected approval times are greater when Democrats control the White House, when the agency's oversight committees are more liberal, and when the House and Senate are more liberal.

H2: The expected approval time for drug *i* is a decreasing function of the political organization of the sufferers of the indication disease *j*.

H3: The expected approval time for drug *i* is a decreasing function of the resource wealth of groups representing disease *j*.

H4: The expected approval time for drug *i* is decreasing in the media coverage of the disease *j* for which it is intended.

H5: The expected approval time for drug *i* is increasing in the disease-specific order of entry.

H6: The *effect* of media and group organization upon expected approval times is increasing in the disease-specific order of entry.

H7: The expected approval time for drug *i* is decreasing in the political clout of the firm *k* producing it.

Empirical Analysis

FDA drug review occurs only after a drug completes Phase I clinical trials (testing for information on drug safety), Phase II trials (testing for effectiveness and safety), and Phase III trials (verification of safety and effectiveness and testing for adverse effects). On average, these trials consume six years of drug development. This is more than half of the time to market (Dranove and Meltzer 1990; Comanor 1986). After Phase III trials,[6] the sponsoring company submits a New Drug Application (NDA) to the FDA. The FDA's Center for Drug Evaluation and Research (CDER) then reviews the NDA by assigning the NDA to a review team composed of doctors, pharmacologists, chemists, statisticians, microbiologists, and other experts. The most novel of these drugs are called "new chemical entities" (NCEs). The dependent variable in the following analyses is the length of the NDA review stage (in months) for an NCE. Summary statistics and brief variable definitions appear in Table 1.

I consciously restrict the sample in two ways. First, I analyze only NCEs, while the FDA screens hundreds of other drugs annually. These include "generic drugs" (simple copies of drugs whose patent protection has expired) and "supplemental" applications which occur when a company seeks to market its drug for a disease

[6]This is a highly cursory summary of the process. See GAO (1995) for more information.

Table 1 Descriptive Statistics for Selected Variables

Variable	Valid N	Mean (Std Error)	Min	Max
Review Time (in months) for all NCEs	453 drugs	45.78 (54.07)	0	221.06
Approval Time (in months) for all **approved** NCEs	298 drugs	25.40 (20.64)	0.59	122.50
World Sales of Firm (yr of submission) [in millions of 1990 U.S. $]	2034 firm-years	3,555 (6,689)	0	57,537
R&D Budget of Submitting Firm (yr of submission) [in millions of 1990 U.S. $]	1698 firm-years	328.1 (514.9)	0	4287.8
Number of Submissions of Submitting Firm (at date of drug's submission)	338 drugs	6.60 (6.15)	1	30
Order of Entry of Drug for Primary Indication Disease, 1977–2000 [= # drugs previously approved for disease at date of submission, plus one]	453 drugs	10.88 (11.67)	1	54
Dummy: Is primary indication of drug a lethal disease?	184 diseases	0.43 (0.50)	0	1
Dummy: Is primary indication of drug an acute disease? [0 = chronic]	184 diseases	0.34 (0.48)	0	1
Avg 1990s U.S. Incidence of Primary Indication Disease [per 1,000 persons]	169 diseases	36.30 (79.83)	0	448.55
Average U.S. Death Rate of Primary Indication Disease [per 1,000 persons]	173 diseases	0.08 (0.31)	0	2.78
U.S. Hospitalizations associated w/ Primary Indication Disease, 1997	184 diseases	109,471.3 (227,726.3)	0	1,156,531
Average Length (in days) of Hospitalizations associated w/ Primary Indication Disease, 1997	184 diseases	3.51 (5.80)	0	54.2
Number of National and Regional Groups representing Sufferers or Advocates of Indication Disease	277 diseases	7.50 (24.96)	0	249
Budget of Group with Largest Budget representing Indication Disease	257 diseases	$22.9M ($77.6M)	$0	$804.4M
Four-year average mentions of indication disease in *Washington Post*, up to and including submission year	450 drugs	101.7 (289.9)	0	3115
Dummy: Orphan Drug [=1]	453 drugs	0.10 (0.30)	0	1

other than the one for which it was originally submitted. Because the review process is very different for these applications, I leave them to another study. Second, the data ignore the clinical trial stage of drug development. I have chosen not to analyze it here because the length of the clinical trial stage depends heavily upon the speed of the company and its clinical testing regime.[7]

[7]Dranove and Meltzer (1994) observe that the length of the IND stage is positively correlated with the length of NDA review. A formal model of product approval with strategic firm submissions is underway (Carpenter and Ting 2001).

Data and Measurement

To measure political influences on the agency, I first include three dummy variables representing partisan control of electoral institutions: (1) a dummy variable scored 1 if Democrats have a majority in the House of Representatives in the year of the drug's submission, (2) a dummy variable scored 1 if the Democrats have a majority in the Senate, and (3) a dummy variable scored 1 if a Democrat is president. To these I add four variables representing the ideology of the median member of the House and Senate, and the ideology of the median member of the FDA's

House and Senate oversight committees, using "inflation-adjusted" ADA scores.

Group Variables (H2, H3). To gauge the political organization of disease sufferers I employ several measures collected from the Gale™ database. For each disease for which a sample drug was reviewed, a research team agreed upon a search term (or set of search terms), and the Gale database was searched under this term.[8] For each disease, I collected data on each organization that was retrieved by the Gale search engine under a term search. This dataset includes over 4,000 groups covering over 300 different diseases. Superfluous organizations with no identifiable relation to the disease were excluded, as were international organizations. From this database I collected the following variables.

To measure the organization of disease sufferers and their advocates (H2), I tabulated the total number of groups representing a disease constituency in the Gale database. Since the Gale database classifies groups as national or regional/local, I conducted this tabulation for *national groups* and for *regional/local groups*. In the statistical analyses below, I include this variable and its square to test for a nonlinear relationship. To test H3, I calculate *the budget of the group with the largest budget* representing the disease. This variable will be zero whenever a disease has no groups. The maximum group budget for the average disease in the sample is 22.9 million dollars in 1998 currency, but for those diseases with nonzero group counts the mean is $62.5 million.[9]

Measuring Media Coverage and Congressional Attention to Disease (H4). Broadly, media coverage of a disease comes in two forms—print and broadcast. To measure print coverage, I consulted the electronic archives of the *Washington Post*, a highly influential newspaper over the past three decades that is the dominant daily reading material of Washington bureaucrats. (All FDA drug approval decisions are made at FDA headquarters in Rockville, Maryland.) To measure broadcast news coverage, I consulted the Vanderbilt TV News Archive, which is also searchable electronically.[10]

To measure print coverage, a research team again agreed upon a list of search terms for diseases and tallied the total number of stories in which a disease was mentioned in a given year. This was done for each disease in the sample (over 300) for each year from 1977 to 2000. Obituaries were excluded, and search terms were adjusted to ensure that superfluous "hits" were excluded. A research team searched under "stroke AND disease" using a Boolean operator, for instance, to avoid hundreds of golf stories. I conducted a similar tabulation for the Vanderbilt database, for each disease yearly from 1977 to 2000.

Diseases get differential emphasis in another crucial venue: Congress. Committees devote whole hearings to discussing scientific progress on a given disease, while other diseases go unmentioned for decades. Using the abstracts of the *Congressional Information Service Annual*, a research team tabulated the number of days of those hearings (House and Senate) where a disease was mentioned in the CIS abstract of the hearing itself.

Order of Entry (H5, H6). To test Hypothesis 5, I include a measure of the order of market entry for a given drug. For each disease I sorted drugs by date of approval. I then tabulated the order in which the drug was approved for the disease that is its primary label indication. (I also included a measure sorting drugs by date of *submission*, which does not change the substantive results of any analyses.) To test Hypothesis 6, I interact this variable with other disease-related variables (group aggregates and media coverage).

Firm Controls (H7). Olson (1997) argues that more experienced firms and more specialized firms receive quicker approval times (but see Olson 1999). I measure firm experience by the number of drugs previously approved for the firm during the sample period (1975–2000). I measure the *research specialization* of a firm by calculating its R&D expenditures as a percentage of its total sales. Because R&D data are difficult to obtain, including this variable reduces sample sizes, and I include it only in reduced models.

Clinical, Medical and Epidemiological Factors. I also employ numerous control variables that incorporate clinical and epidemiological data on diseases. I gathered data on

[8]The Gale Associations Unlimited database (at http://www.galenet.com/servlet/AU) contains data on approximately 460,000 international and U.S. national, regional, state, and local nonprofit organizations in all fields, including IRS data on U.S. 501(c) nonprofit organizations. A list of diseases and corresponding search terms is available upon request.

[9]I have estimated models with two discrete measures of political activity based upon data from Gale and the Center for Responsive Politics (CRP). Neither measure was significantly associated with review times. Results are available upon request from the author.

[10]These measures rely on disease coverage *before the drug's submission*, so endogeneity of media coverage to drug approval is ruled out. If anything, drugs that are approved more quickly should result in the media having less time to cover them before they are approved.

disease incidence from the Centers for Disease Control (CDC) and the *Health Yearbook of the United States*. For rare conditions such as Wilson's disease, these data are difficult to obtain, and incidence data account for many missing observations in the estimations below. Using available incidence and prevalence data, I also calculate three dummy variables measuring whether the disease primarily affects men (e.g., male pattern baldness), women (ovarian cancer) and children (neonatal respiratory difficulties), in the sense of over 90 percent prevalence in one of these categories.

The *severity* or "burden" of a disease is also a crucial factor (Vogel 1990, 459–461). Accordingly, I include the *death rate* per 1,000 U.S. inhabitants of the disease. I also calculate a *lethal disease* dummy variable, which indicates whether the disease killed more than one person per year in the 1990s. I also include the *number of hospitalizations* and the *average length per hospitalization* for diseases, using the Healthcare Cost and Utilization Project (HCUP) discharge data of the Agency for Healthcare Research and Quality (http://hcup.ahrq.gov/HCUPnet.asp). The average fiscal cost of a hospitalization is also available, but this is highly correlated with average length of hospitalization (rho = 0.90) and was excluded. Consistent with Quirk's (1980) argument that the FDA values its staff resources more than its fiscal resources, I include the staff level of CDER in all analyses.

Methodology

I test Hypotheses 1 through 7 using maximum-likelihood duration analysis. The optimal stopping model offers a helpful guide to empirical analysis because it predicts the form of the hazard function. Because drug approval has costly reversibility, the agency's optimal stopping policy is characterized by scarcity of quick approval, rising approval, and then falling approval (not all drugs get approved). In other words, *the hazard of drug approval is nonmonotonic*, rising from zero to a unique mode, then returning to zero. This fact rules out commonly used distributions such as the Weibull and Gompertz. For this reason, I employ the log-normal distribution as a functional form.[11]

Finally, because I cannot possibly measure every variable that is relevant to FDA drug approval—particularly the actual quality or danger of the drug—my statistical analyses include a "frailty" parameter that captures unobserved heterogeneity in drugs (Box-Steffensmeier and Jones 1997). Again the stopping model is helpful in selecting the functional form of this frailty. Conditioned on unobserved drug danger (μ), the first-passage time distribution is inverse Gaussian (Karatzas and Shreve 1991, 80, 197), and so I select the inverse Gaussian distribution as the frailty distribution.

[11]Using either the generalized *F* or gamma distribution makes no difference to the results.

Results: The Insignificance of Oversight Correlates

Table 2 includes a larger-sample estimation in Model 1, while Model 2 adds firm and group-budget variables for which measurements are difficult to obtain.[12] Marginal effects from two reduced models appear in Table 3. The first result of note from Table 2 disconfirms Hypothesis 1. Approval times appear insignificantly related to the partisanship and ideology of the FDA's elected overseers in Congress and the White House. The coefficient estimates are not consistently positive, as hypothesized. Moreover, across all estimations these coefficient estimates are statistically indistinguishable from zero. A partial exception to this pattern is that, in Table 2, a Democratic Senate appears to be associated with *quicker* approvals, not slower ones. Yet this effect is barely differentiable from zero at a $p < 0.10$ significance level. The coefficient estimate for this variable is not significant in other regressions, and even switches sign when firm variables are added (analyses available upon request). The overriding lesson of the estimations is that institutional variables provide little if any explanatory power in FDA drug review. Hence they are dropped from further analyses.

These estimates do *not* necessarily imply the political independence of the FDA or the lack of partisan, congressional, or presidential influence over FDA drug approvals. It may be that Republicans and Democrats tend not to disagree strongly over the protection-provision tradeoff. In the 1970s and early 1980s, Republicans and Democrats alike favored a stringent policy. In the last decade, both parties have pressed for faster approvals.

The Salience of Disease Organization and Media Coverage

Estimates for the group and media coverage variables in Table 2 elucidate the importance of disease-specific waiting costs. The first result of note is that drug review times are a nonmonotonic function of the number of groups representing a disease. Approval times first *rise* as the number of disease groups climbs, then fall again as the number of groups gets large. This result disconfirms Hypothesis 2. Figure 1 offers a graphical depiction of the relationship between expected approval times and disease groups, based upon marginal effects estimates from a reduced model (see Table 3, Model 1). Diseases with few representative organizations such as ulcerative colitis and lymphoma are advantaged by this relationship, as are diseases with a very large number of groups such as diabetes. The estimated function reaches a maximum

[12]The addition of several variables—including firm and disease group correlates—often appreciably reduces sample sizes. To check for robustness, I estimate models with different combinations of these variables. I have also estimated models with some "time-varying covariates" where the regressors (oversight variables, media coverage, group aggregates) vary over the course of drug review. None of the substantive results below are affected by this method of estimation. These results are available upon request from the author.

TABLE 2 FDA Review Duration Models for NCEs, 1977–2000
[Log-normal duration analyses (MLE), assuming inverse Gaussian frailty.]

Variable	Model 1	Model 2
Constant	2.9009+ (1.6655)	4.7209** (0.2938)
Oversight (Keyed to Year of Drug Submission)		
Median Adjusted ADA Score, House Comm	−1.9803 (2.4440)	—
Median Adjusted ADA Score, Senate Comm	−0.9256 (1.5307)	—
Median Adjusted ADA Score, House Floor	1.0518 (5.7561)	—
Median Adjusted ADA Score, Senate Floor	0.6424 (1.7415)	—
Democratic House Majority [0,1]	0.4376 (1.3900)	—
Democratic Senate Majority [0,1]	−0.9107+ (0.4651)	—
Democratic President [0,1]	−0.3477 (0.2877)	—
Clinical/Epidemiological Factors (Keyed to Primary Indication)		
Incidence of Primary Indication [per 1000]	**0.0012*** (0.0005)	**0.0023**** (0.0008)
Primary Indication is Lethal Condition [0,1]	−0.0465 (0.1723)	−0.1828 (0.1599)
Death Rate, Primary Indication [per 1000]	**−0.4260*** (0.1807)	−0.2177 (0.1507)
Primary Indication is Acute Condition [0,1]	−0.1530 (0.1776)	−0.0797 (0.1480)
Primary Ind. results in Hospitalizations [0,1]	−0.1450 (0.2008)	−0.3219 (0.1874)
Millions of Hospitalizations assc w/ Indication	**1.4506**** (0.4300)	0.0039 (0.0581)
Average Length of Hospitalizations (Days)	−0.0110 (0.0149)	−0.0253 (0.0155)
Disease Mainly Affects Women [0,1]	−0.3872 (0.2687)	−0.1641 (0.2090)
Disease Mainly Affects Men [0,1]	0.0437 (0.3042)	0.2154 (0.2939)
Disease Mainly Affects Children [0,1]	−0.2175 (0.3267)	−0.2187 (0.3460)
Orphan Drug [0,1]	−0.2613 (0.1645)	−0.0618 (0.1370)
Disease Politics: Group and Media (Keyed to Primary Indication)		
National & Regional Groups, Disease	**0.0147*** (0.0065)	**0.0181**** (0.0062)
(National & Regional Groups)^2	**−0.00007*** (0.00003)	**−0.00007*** (0.00003)
Nightly TV News Disease Stories, 4-Year MA	0.0155 (0.0115)	—
Maximum Group Budget ($B), Disease	—	−0.3267 (1.1143)
Max Group Budget ($B) × Order-of-Entry	—	**−0.2151**** (0.0958)
Washington Post Disease Stories, 4-Year MA	**−0.0038*** (0.0011)	**−0.0019**** (0.0006)
Days of Cong Hrgs on Disease, 4-Year MA	0.0102 (0.0132)	−0.0142 (0.0154)
Order of Disease Market Entry for Drug *i*	**0.0186**** (0.0056)	**0.0597*** (0.0237)
Firm and FDA Variables (Keyed to Year of Drug Submission)		
Previous Approvals, Submitting Firm	—	**−0.0192*** (0.0080)
FDA drug review (CDER) staff [FTEs]	−0.0001 (0.00063)	−0.0015** (0.0002)
ln(σ) [log–normal shape]	−0.4701** (0.1135)	−0.3786** (0.0737)
ln(θ) [frailty/heterogeneity]	0.5875 (0.4716)	−1.3497* (0.6424)
Number of Reviewed (Approved) Drugs	408 (262)	300 (249)
Log–likelihood	−442.1061	−327.3282
χ^2_k (Prob.)	206.75 (0.0000)	126.98 (0.0000)

Note: Dependent variable is log of approval time, from NDA submission to approval, in months. Asymptotic standard errors in parentheses. ** implies significance at $p < 0.01$; * implies significance at $p < 0.05$; + implies significance at $p < 0.10$. (All tests are two-tailed.) "Primary Indication" is main disease/condition for which drug is submitted. Model 2 includes group budget variable and firm variables for which data are difficult to obtain.

TABLE 3 Marginal Effects and Elasticity Estimates
Marginal Effects for one-unit increase in variable, followed by elasticities [in brackets].

Variable	(1) *w/o* Firm or Group Budget Variables (450 drugs)	(2) *with* Firm & Group Budget Variables (300 drugs)
Incidence of Primary Indication [per 1000]	**0.0590 [0.2147]**	**0.0442 [0.1275]**
Primary Indication is Lethal Condition [0,1]	-0.1303 [-0.0026]	-3.4486 [-0.1172]
Death Rate, Primary Indication [per 1000]	**-11.2471 [-0.0339]**	-4.1228 [0.0247]
Primary Indication is Acute Condition [0,1]	-6.0350 [-0.0736]	-1.6645 [-0.0255]
Primary Ind. results in Hospitalizations [0,1]	-2.6177 [-0.0652]	5.9066 [0.2394]
Millions of Hospitalizations assc w/ Indication	**0.00004 [0.1660]**	0.7350 [0.0043]
Average Length of Hospitalizations (Days)	-0.6916 [-0.1186]	**-0.5120 [-0.3119]**
Disease Mainly Affects Women [0,1]	-4.3826 [-0.0070]	-3.5245 [-0.0127]
Disease Mainly Affects Men [0,1]	1.0718 [0.0009]	4.4913 [0.0068]
Disease Mainly Affects Children [0,1]	-1.3442 [-0.0017]	4.9285 [0.0081]
Orphan Drug [0,1]	-2.3997 [-0.0095]	0.9470 [0.0073]
National & Regional Groups, Disease	**0.5577 [0.2969]**	**0.3562 [0.3852]**
(National & Regional Groups)^2	**-0.0026 [-0.0966]**	**-0.0015 [-0.1214]**
Washington Post Disease Stories, 4-Year MA	**-0.0781 [-0.1682]**	**-0.0373 [-0.1614]**
Order of Disease Market Entry for Drug *i*	**0.4697 [0.1582]**	**1.1618 [0.5480]**
Max Group Budget ($B) x Order-of-Entry	—	**-3.9209 [-0.3363]**
Previous Approvals, Submitting Firm	—	**-0.3860 [-0.1215]**
FDA drug review (CDER) staff [FTEs]	**-0.0531 [-2.2117]**	**-0.0306 [-2.0868]**
Firm R&D as Percentage of Sales*	—	0.0045 [0.0353]
Mean of Predicted Dependent Variable [FDA Approval Time]	31.3 months	20.0 months

Note: Estimates extracted from unreported reduced model with same covariates; actual coefficient estimates available from author. Z-scores for marginal effects and elasticity estimates are virtually identical to those for coefficients from basic model. For all variables reported here, where a variable's coefficient estimate is statistically significant in the originally estimated model, both the marginal effect estimate and the elasticity estimate are also statistically significant above. *Firm R&D variable not in basic reduced models; marginal effects estimate retrieved from another model. Dependent variable is log of approval time, from NDA submission to approval, in months. Negative estimates indicate reduction in expected review time.

at 107.25, where for instance Parkinson's disease would be located with 107 groups. Perhaps not coincidentally, drugs for Parkinson's—*Comtan* (21.53 months), *Tasmar* (19.89 months) and *Requip* (20.58 months)—have received slower-than-average approvals in the late 1990s (the average NCE approval time was 13.3 months in the period when these three drugs were approved).

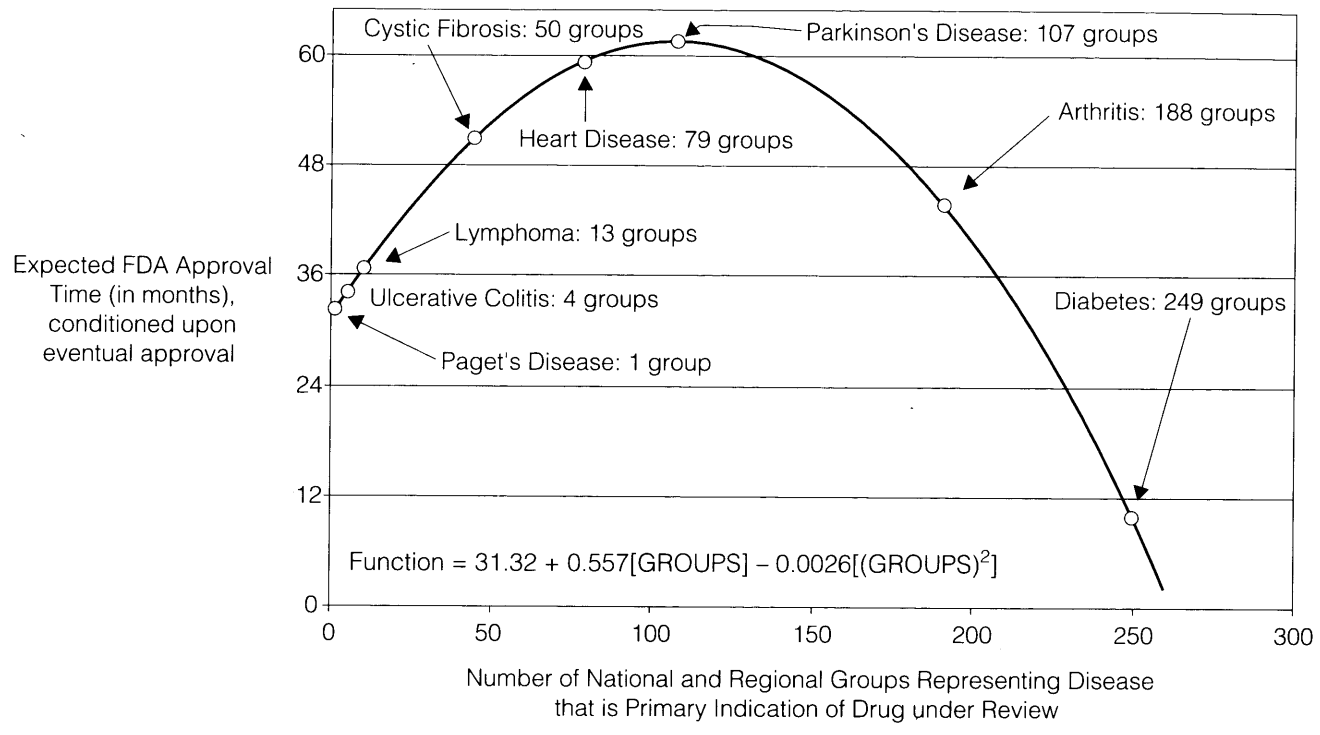
Why nonlinearity? Lobbying the FDA for quicker approvals requires collective action among groups. The greater the number of groups, the more difficult such cooperation becomes (Olson 1971). Salisbury et al. (1987)[13] and Baumgartner and Jones (1993; Chapter 9) suggest that collective action can be frustrated when many groups compete for organizational leadership in a policy domain. Hence more groups may not always lead to greater waiting costs for the FDA. A few highly focused groups (such as in the AIDS case in the 1980s) may be better able to overcome collective action problems in lobbying federal agencies, hence imposing higher waiting costs than a set of more numerous organizations.[14]

The apparent effect of *print* media coverage of disease is equally robust, producing negative and statistically significant estimates in all analyses, in support of Hypothesis 4. The media coverage variable is a four-year

[13]Salisbury and colleagues note "a general tendency toward interest proliferation and fragmentation as the interests of various types of producers . . . grow increasingly differentiated" (1987, 1219). Baumgartner and Jones make this point with more explicit reference to the number of groups operating in a policy domain (1993, 179–184).

[14]The stopping model could be amended to achieve consistency with this result, but it would require replacing the additive political multiplier in the current version $[\psi_j = f(M_j + \mathbf{W}_j)]$ with a more generalized functional form $[\psi_j = f(M_j, \mathbf{W}_j)]$. This would, of course, be a different model. I thank an anonymous reviewer for this suggestion.

FIGURE 1 Expected FDA Approval Time as a Function of Groups Representing Disease



moving average of stories mentioning a disease in the *Washington Post* (the four years preceding the drug's submission).[15] Generally, *Post* disease coverage is a weakly nonlinear function of the number of disease-related groups, peaking for diseases in the low to moderate range of the groups distribution, and for diseases without wealthy umbrella associations. (*Post* coverage is, however, high for some diseases with wealthy peak associations, such as diabetes). At the margin, then, media coverage thus seems to benefit those disease sufferers who are either weakly politically organized (e.g., Parkinson's, asthma) or very highly organized (Alzheimer's, breast cancer).

Broadcast media attention to disease—as measured on the nightly newscasts in the Vanderbilt database—does not appear to be significantly associated with reduced review times. The same is true for congressional hearings on a given disease, which also appear to be insignificantly related to drug approval times.

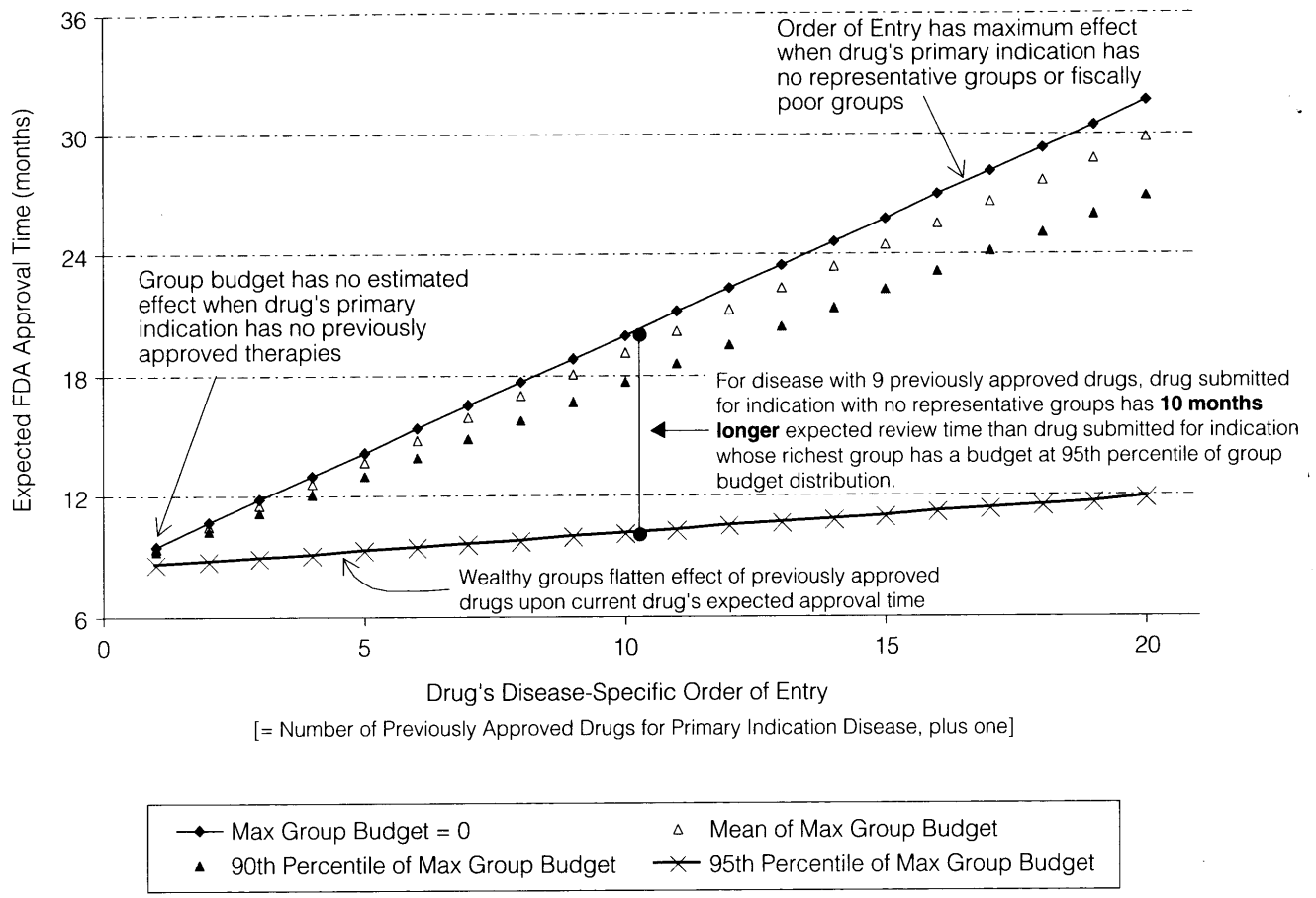
The greater relative influence of print media over broadcast media is puzzling at first glance. I offer two possible explanations. First, FDA personnel receive information about the salience of particular diseases through numerous channels, but they probably pay more attention to "authoritative" news sources such as the *Post* and the *New York Times* than they do to TV news. Major print newspapers affect TV news coverage more than TV news affects major newspaper coverage (Bartels 1996), and FDA personnel are likely concerned not only with what the general public is consuming, but also with what *politicians* and *political elites* are paying attention to. A second (perhaps more important) reason is that disease mentions on the nightly newscasts of the major networks are few and far between. As a result, the measures for TV news coverage of disease are very crude and discontinuous. This does not necessarily mean that the measure is a bad one. It rather reflects the very tight time budgets of the nightly news. Unless a given disease is the major issue of the day (something that has happened only occasionally for diseases such as AIDS), most diseases do not receive attention from the broadcast networks. Agenda-setting influences on the FDA are less likely to work through TV news than through print media.

[15]Four years was not chosen for any particular reason other than that sustained attention is necessary for a problem to become salient in agenda-setting politics (Baumgartner and Jones 1993; see also the notion of issue recurrence in Hansen 1991). Results using other averages are substantively identical and are available from the author upon request.

The Importance of Firm Characteristics

The results are consistent with those of Olson (1997); review times are a decreasing function of the firm's prior experience. In analyses that are not reported, review times appear to be an increasing function of R&D as a percent

FIGURE 2 Disease Group Budgets Dampen Order-of-Entry Effects



of sales (see Table 3 for a marginal effects estimate). Although this effect is statistically significant, its estimated marginal impact is extremely small (see Table 3).[16]

Clinical and Epidemiological Controls. Two findings from coefficient estimates on the medical control variables are of interest. First, drugs treating diseases with greater incidence or prevalence in the general population are approved *more slowly*. This may seem surprising, yet conditions such as the common cold, influenza, and Poison Ivy are extremely common but command less political emphasis than do rarer but deadlier conditions. Second, approval times are a decreasing function of the severity of the primary indication, as measured in the disease-specific death rate or the average length of hospitalizations.

Order-of-Entry Effects (H5 and H6). FDA drug approval reflects one overriding fact: *the political demand for any drug depends upon its order of entry into a disease-specific market.* When many drugs have been approved for a medical condition, the FDA will find it less costly to wait upon a new drug for that disease. There is an "early-entrant" effect in FDA regulation as seen by the positive and generally statistically significant coefficient on the order of entry variable. Specifically, a one-standard deviation increase in the disease-specific order of entry for a drug is associated with three to seven months increase in expected approval time (see Table 3). In reduced models, the order-of-entry variable has one of the largest elasticities in this study. A ten-percent increase in this variable is associated with a 1.6 percent to 5.5 percent rise in approval time. These results support Hypothesis 5. An example of these effects occurred for early AIDS drugs. The first drug for AIDS—azidothymidine (AZT)—was approved more quickly than subsequent therapies, in part because pressure for quick AIDS drug approvals subsided after AZT's approval (Epstein 1996).

Table 2 also shows that the effect of maximum group budget is not *increasing* in order of entry but is instead *decreasing*. This disconfirms Hypothesis 6 but offers a theoretically interesting lesson in its own right. The effect of having a single group with a large budget is greatest

[16]See Carpenter and Turenne for other firm-level effects on FDA drug approval (2001).

not when the first drug for that disease is being submitted, but when many drugs already exist (see Figure 2). This is the only manner in which disease-group budget matters to drug approval; H3 is disconfirmed in all estimations. This result may be interpreted in two ways. First, when a number of drugs are already approved for a disease, disease-specific advocates for quick approvals may face a greater collective action problem in further lobbying. Yet groups with large budgets may be able to overcome this dilemma. The American Heart Association may be better able to lobby for faster approvals for, say, the tenth drug for hypertension; groups such as the National Gaucher Foundation are less able to lobby for quick approvals for additional Gaucher's Disease drugs.

A different interpretation is that, whatever advantages disease-specific groups with large budgets have in FDA drug approval, these advantages vanish when few or no prior drugs have been approved for the disease. In these instances, order-of-entry effects dominate. According to the model, "poor" disease advocates are no worse off than "rich" disease advocates when the disease has few or no existing pharmaceutical treatments.

Marginal Effects

Marginal effects estimates for the "best" models—in the sense that their estimates are consistent and significant across analyses—appear in Table 3. In log-linear regressions these models explain 28–30 percent of the variance in approval times.

The largest effects emerge in disease-specific variables. A standard deviation increase in *Washington Post* coverage of a disease (290 more stories per year over a four-year period) is associated with a decline of ten to twenty-two months in approval time for drugs treating that disease. A standard-deviation increase in the market order-of-entry for a drug—equivalent to eleven spots in an entry ranking—adds over a year (13.6 months) to expected approval time. This effect is tempered, however, by the wealth of disease advocates (see Figure 2). In essence, the effect of order-of-entry is eliminated for drugs that treat patients with well-heeled lobbies and exists mainly for those drugs whose intended consumers lack the political luxury of a large, resource-rich group voicing their cause.

The size of the staff of CDER is negatively related to FDA approval times in all estimations. Every 100-person increase in CDER staff is associated with a three- to five-month reduction in expected drug approval time. Much of the increase in CDER staff has been driven by the Prescription Drug User Fee Act of 1992, which financed an employment boost by requiring per-application "user fees" from drug companies. It is difficult, however, to attribute this Act to any single coalition or participant in pharmaceutical politics. An increase in CDER staff had long been requested by the FDA, drug companies and patient groups alike favored the legislation, and the Act passed the Senate unanimously.

Conclusion

FDA drug approval is an exercise in learning over time. Because the structure of the drug approval decision entails a choice over timing behavior, drug approval is a process in which the benefits and costs of waiting to learn will shape whether certain drugs get approved more or less quickly than others.

Does "politics" affect FDA drug approval? Is there political influence over the speed of FDA drug review? The answer is clearly "yes," but it depends entirely on the form of politics we consider. Partisan politics and ideological politics play less of a role in product approval because the costs and benefits of waiting are case-specific. If the controversies over AIDS drugs in the 1980s suggest anything, it is that citizen groups and the media have a powerful impact upon regulatory outcomes. It is noteworthy that group organization and media coverage of disease are strongly associated with approval times even though the models control for eleven disease-specific clinical and epidemiological variables. Unfortunately, there has been little research on these questions in contemporary political science. While focus on partisan and ideological politics is necessary and helpful, the statistical estimates presented here show that the party and ideology of "principals" do not hold all the answers to explaining important public policy outcomes. Indeed, oversight ideology and partisanship are consistently insignificantly associated with FDA review times. The politics of bureaucratic decision making is instead disease-specific.

It is possible that ideology plays a role different from its conceptualization here (partisan or left-right ideology), in the sense that deregulation unites consumer-oriented liberals (like Edward Kennedy) and deregulation-oriented conservatives (Orrin Hatch). In this respect, it is worth noting that Hatch and Kennedy wrote the PDUFA of 1992. Still, the primary quickening effect of PDUFA seems to have come from the staff boost that it gave to CDER, at least according to the empirical analyses above. While PDUFA had some deregulatory features, increasing the number of FDA bureaucrats by imposing industry user fees is an initiative not fully reconcilable with deregulation.

Contributions of the Stopping Model and Agenda-Setting Scholarship

The stopping framework used in this article has several advantages. First, it clarifies the learning process by which uncertain bureaucrats review new products. In this way, FDA decisions can be compared to a wide variety of learning problems faced by other agencies. Second, the combinatoric elements of equation (3) demonstrate the importance of drug-specific order of entry, not only by itself but also for shaping the influence of other variables.

Yet some of the most important insights into FDA approval politics come from theories of group cooperation and agenda-setting (Salisbury et al. 1987; Baumgartner and Jones 1987). There is, of course, some complementarity between the formal stopping model and agenda-setting theories. The stopping model focuses upon bureaucratic mechanisms, while theories of group cooperation and agenda-setting point to mechanisms of political influence. Recognizing the case-specific waiting costs of bureaucratic timing decisions allows us to reconceive media and interest group influence in bureaucratic politics.

Appendix

Proofs

Proof of Proposition 1: For simplicity I assume $\alpha = 1$ throughout. The solution to (4) must satisfy the functional (Bellman) equation,

$$\delta F(\hat{\mu},t) = \left\{ E_{\dot{\mu},t} F(\hat{\mu}(t+dt)) - F(\hat{\mu}(t)) \right\} + o(dt) \qquad \text{(A-1)}$$

where $o(dt)$ represents an "omicron term" (including terms of higher order than t that vanish more quickly than terms of order t as dt goes to zero). Dropping higher-order terms and using Ito's Lemma to Taylor expand the expectation term (Taylor and Karlin 1998),

$$\delta F(\hat{\mu},t) = \left\{ E_{\dot{\mu},t}\left[F(\hat{\mu}(t+dt)) - F(\hat{\mu}) \right] \right\}$$

$$= E(dF) = F_t(\hat{\mu},t) + \tfrac{1}{2}\frac{S(t)^2}{\sigma^2} F_{\dot{\mu}\dot{\mu}}(\hat{\mu},t)$$

$$F_t(\hat{\mu},t) + \frac{S(t)^2}{2\sigma^2} F_{\dot{\mu}\dot{\mu}}(\hat{\mu},t) - \delta F(\hat{\mu},t) = 0 \qquad \text{(A-2)}$$

At the optimal stopping barrier, the following conditions must hold (Dixit 1993).

$$F(\hat{\mu},t) = A - \mu^*/\delta \qquad \text{(value matching)}$$

$$\frac{d}{dt}F(\hat{\mu},t) = F_t(\hat{\mu},t) = \frac{d}{dt}\left[A - \mu^*/\delta\right] \qquad \text{(smooth pasting)}$$

The time-derivative of the stochastic value function is simply the first term of (A-2). The time-derivative of the stopping payoff is $d\left[A-\mu^*/\delta\right]/dt = 0 \Rightarrow F_t(\hat{\mu},t) = 0$. To retrieve the barrier $\eta(t)$, rewrite (A-2) to satisfy the smooth pasting condition and evaluate $F(\hat{\mu},t)$ according to the value matching condition, to get

$$\frac{S(t)^2}{2\sigma^2} F_{\dot{\mu}\dot{\mu}}(\hat{\mu},t) - \delta\left[A - (\mu/\delta)\right] = 0 \qquad \text{(A-3)}$$

Finally, evaluate (A-3) at $\hat{\mu} = \eta(t)$, such that

$$\eta(t) = \delta A - \frac{S(t)^2}{2\sigma^2} F_{\dot{\mu}\dot{\mu}}\left[\eta(t),t\right] \qquad \text{QED}$$

Proposition A-1: A formal example of order-of-entry effects and interactions. For any disease $j = J$, consider a sequence of disease-specific drugs $i = 1,\ldots N_J$. Then $\gamma_{i,J}$ is the curing probability for drug i for disease J. Let $f(\gamma)$ be a stationary curing distribution for any disease, such that $E[\gamma_i] = g$ for all $i \in J$. Then by the law of iterated expectations, the expected approval payoff for the N_J-th drug can be written

$$E_i\left[A_{N_J,J}\right] = E_i\left[\lambda_k \psi_J L_J \left\{\gamma_{N_J}\right\} \prod_{i=0}^{N_J-1}\left(1-\gamma_{i,J}\right)\right]$$

$$= \left\{\lambda_k \psi_J L_J g\right\} \times (1-g)^{N_J-1} \qquad \text{(A-4)}$$

The first derivative of $E_i[A_{N_J,J}]$ with respect to N_J is

$$\frac{dE_i\left[A_{N_J,J}\right]}{dN_J} = \ln(1-g) \times \left[\left\{\lambda_k \psi_J L_J g\right\} \times (1-g)^{(N_J-1)}\right] \qquad \text{(A-5)}$$

All terms in (A-5) are positive but for $\ln(1\text{-}g)$, which is negative ($\gamma > 0$). So the approval payoff is decreasing in N_J, which restates **H5**, and the expected approval time is increasing in N_J. But notice that the derivative is also a function of ψ, which gives **H6**. **QED**

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