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Why Do Bigger Firms Receive Faster Drug Approvals?

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ABSTRACT

We test several explanations for the commonly observed pattern that larger firms receive shorter FDA approval times for the drugs they submit. Candidate explanations include capture and rent-seeking and "external-signals" accounts. Analyses of 766 new molecular entities submitted to the FDA from 1979 to 2000 suggest that large-firm advantage in pharmaceutical regulation is primarily due to two factors: (1) enhanced regulator familiarity with large firms by virtue of their submission histories (an effect augmented when firms merge), and (2) regulatory favor for "early entrants" to a disease market, which is induced from disease-specific consumer pressure for approvals. Our analyses show that as much as 70% of observed large-firm advantage in expected FDA approval times can be attributed to these factors, 30-55% to familiarity alone. We find no consistent support for rent-seeking or "political clout" explanations.

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For the better part of three decades, the idea that regulation benefits larger producers at the expense of smaller ones has been a staple conclusion of scholarship in political economy (Huntington 1955, Stigler 1975, Bartel and Thomas 1987; Viscusi 1992). Large firms enjoy relative advantages under numerous forms of regulation – ranging from price-setting institutions to content regulation [e.g., the Federal Communications Commission] to "consumer safety" measures. Such advantages appear in numerous industries, ranging from transportation (Rothenberg 1994) to telecommunications (Noll 1973; Crandall and Flamm 1989) to pharmaceuticals (Grabowski and Vernon 1983). In all of these studies (and many others), researchers have found evidence for the social-scientific proposition that, indeed, "size matters."

The apparent consensus underlying the regulatory advantages of larger firms masks considerable scholarly discord as to why it exists. In other words, there is relative agreement about the *fact* of large-firm advantage, but little accord about the *mechanism* that accounts for it. The dominant explanation for this pattern remains that of political capture, rent-seeking or "predation by regulation" – the idea that larger firms apply implicit or explicit political pressure in order to influence the regulatory process in their favor and impede smaller firms' access to the market (Stigler 1975; Bartel and Thomas 1987). More recently, "external signals" approaches have emerged (Joskow 1974; Noll 1985; Olson 1996, 1998, 1999), positing that regulators use firm characteristics such as size, capitalization and specialization as proxies for otherwise unobservable attributes of the firm's quality.

In this paper we test these explanations in an empirical analysis of pharmaceutical regulation by the U.S. Food and Drug Administration (FDA). Pharmaceutical regulation presents one of the most oft-cited examples of large-firm advantage. Several analyses of the 1962 Amendments to the Food Drug and Cosmetic Act have argued that new constraints placed upon the pharmaceutical industry in the early 1960s adversely affected pharmaceutical productivity (Peltzman 1973;

Grabowski and Vernon 1983), especially for smaller firms (Thomas 1990). More recently, Olson (1997, 1999) has found that several correlates of established firms – including specialization, research intensity, and employment – correlate with quicker drug approvals.[1]

We focus on the most important outcome for firms: the time that the FDA (as gatekeeper to the pharmaceutical marketplace) takes to approve new products, if indeed market entry is granted at all. We conduct duration analyses of regulatory review times for a sample of 766 drugs submitted to the FDA from 1979 to the present. In three ways, our paper differs materially from previous efforts to test economic and political influences upon FDA drug approval. First, our sample is unique in several respects. Most critically, it includes *non-approved drugs*. Drugs that have not been approved – those that are withdrawn by firms, those that are deemed "not approvable" by the agency, or those that *will* be approved but have not *yet* been approved – are uniformly excluded from academic studies of drug regulation.[2] The results of this exclusion, as we show, almost certainly generate misleading inferences. Indeed, large-firm advantages in time-to-approval are *greater* when unapproved drugs are taken into account than when they are not. Our sample also includes more drugs, considered over a longer period of time, than has been studied in past analyses; this added depth of our sample allows for bureaucratic learning and early-entrant protection to set in.

Second, we put prevailing hypotheses – particularly "capture" – more directly to the test than previous authors have done. We gather data on pharmaceutical firms' lobbying budgets, their ownership and merger status and their domestic or foreign status to generate testable hypotheses about whether correlates of firm clout are in fact associated with reduced approval times.

[1] Olson (1999) finds that the firm advantage has disappeared in recent years with the FDA. We discuss this finding at more length below.

[2] The unique exception to this pattern was the GAO's 1995 analysis of drug review times at the FDA. Unlike the GAO study, we combine unapproved and approved drugs in the same sample.

Third, we operationalize and test hypotheses that numerous observers of drug regulation have advanced (albeit informally) regarding the importance of *organized consumers* in drug regulation. Our results show that consumer politics – the differential organization of disease sufferers and their advocates – can serve to reduce large-firm advantage in FDA approval. We also show that, in some cases, consumer politics may enhance large-firm advantages because large firms may be better at targeting drugs to well organized patient groups.

In our analysis, we consider two alternative explanations for large-firm advantage in pharmaceutical regulation (see Carpenter 2001). *Bureaucratic learning* benefits those interests who appear most frequently before the agency, which larger firms that produce a greater number and variety of drugs are more likely to do. *Political pressure from organized consumers* (e.g., AIDS protesters in the 1980s) also leads to regulatory favor for firms who enter the market first, or "early-entrant protection." In what follows, we test different models of firm advantage systematically against one another. Our theoretical alternatives are related to the "external signals" approach but differ in several respects. In Olson's (1997) argument, firm attributes are signals of otherwise unobserved product quality. In the argument we present, firm attributes signal *firm-specific effects* on product quality (or safety), and "familiar" firms may have advantages even if they have below-average safety records. In addition, neither "external signals" theory nor any other theory has predicted the early-entrant protection that we hypothesize here.

1. Explanations for Large-Firm Advantage in Drug Regulation

A. Capture, Rents and "Political Clout." One obvious explanation for why larger firms receive regulatory favor is that politics is involved. The capture theory of regulation predicts that existing firms in any industry attempt to use regulation to erect entry barriers to their potential competitors. Strict variants of capture theory have lost favor to "group" and rent-seeking theories in

recent years, theories which recognize the diversity of interests among producers in any given industry and which admit that consumers, too, can organize. Under either the capture or the rent-seeking theory, however, quicker product approval for larger firms is a decisive entry barrier that these theories can explain. Since entry in the pharmaceutical industry requires prior approval by a government regulator, any relative delay in approval for a smaller firm equates to a financial advantage for larger firms.

Despite the prevalence of capture explanations for large-firm advantage in regulation, they have rarely been tested directly, and pharmaceutical regulation marks no exception to this pattern. Many scholars, upon observing large-firm advantage in regulation, assume capture or rent-seeking occurs (e.g., Bartel and Thomas 1990: 241-42). Olson (1997) suggests that her variables may capture "firm clout," yet she does not directly attempt to measure this variable. In short, there has been no systematic and direct attempt to test rent-seeking theories in drug approval.

B. External Signals to the Regulator. Other analysts point to alternatives to capture as an explanation for why larger firms might do better in the regulatory process. One possibility, suggested by political scientists and economists for several decades now (Joskow 1974, Noll 1985), is that firm size – and related characteristics such as capitalization, research intensity and specialization – proxy for an expected product quality differential about which the regulator is uncertain. This "external signals" approach helps to explain a number of stylized facts about regulation, not only why larger firms receive more favorable regulatory outcomes, but why agencies like the FDA are influenced by consumer letters (Olson 1995). Just as important, recent research suggests that firm advantages can be ameliorated through institutional design of bureaucratic incentives (Olson 1999).

Olson (1997) finds systematic evidence for the external signals explanation of large-firm advantage in a regression analysis of drugs approved from 1990 to 1992. Controlling for clinical factors and FDA priority ratings, Olson finds that firms with greater R & D, greater employment

and a greater number of FDA product applications receive shorter approval times for their drug applications. A 1995 study by the General Accounting Office (GAO) also finds that firms with more submissions receive shorter review times (1995:32). Employment and submissions are doubtless correlated with firm size. Olson (1997) construes these results to mean not that larger firms capture drug regulation, but rather that a rational agency interprets size-related firm characteristics as signals or correlates of unobserved product quality.

2. Early-Entrant Protection and the Advantage of Familiarity

We commence with two observations. First, the FDA has long behaved as if there were immense costs to committing a Type II error – that is, approving a drug that should not have been approved for safety reasons. Moreover, there is little evidence to suggest that this basic commitment to safe approvals has been surrendered in recent years even as drug approval times have shortened. Second, drug approval is significantly affected by pressure from organized patients and their advocates. The case of AIDS drugs in the 1980s is instructive but by no means isolated. As Dranove and Meltzer (1994) show, the FDA gave quicker approvals to drugs for more "important" diseases well before AIDS came along. When disease sufferers are well organized and their cause is highly publicized, anecdotal evidence strongly suggests that the FDA is likely to review drugs for that disease quickly.

Familiarity and early-entrant protection, we argue, undergird large-firm advantage in pharmaceutical regulation. Drug approval presents FDA regulators with a politically charged learning problem. The agency waits to approve until enough evidence has been amassed to show that the drug's benefits outweigh its costs. From the FDA's standpoint, however, drug approval is reputationally irreversible. Once a "bad" (unsafe) drug is approved, nothing the FDA does will

ameliorate the damage to its reputation. A quick recall will not help, and might inflate the damage through its implicit admission of error.

Given this recognized irreversibility of approval, there is little reason for the agency to approve a drug immediately upon its submission. Waiting for more information (and for more review time) always has value, particularly when little is known about the drug, or when it is first submitted. Elsewhere (Carpenter 2002, 2004) we have used this logic to formalize the drug review problem and derive predictions about when large firms will enjoy regulatory advantages. Here we supply the basic intuition underlying our argument.

Bureaucratic Learning and the Logic of Familiarity: Suppose firms differ in the care with which they generate and manufacture products. Some firms, for instance, may have developed better procedures for detecting product hazards. If FDA cannot observe such a firm-specific effect on product quality directly, but can learn about it, then firms that have submitted more products to the FDA are systematically advantaged because the agency's decision-makers know about them. In essence, the agency's "prior beliefs" about a firm are better fixed for large firms than for small firms, and so larger firms face a shorter hurdle of uncertainty at the agency. Indeed, the advantage of familiarity should hold even under some cases where a firm has a safety record that is slightly below industry average. To a point, familiarity can outweigh a poor reputation.

[Figure 1 about here.]

Consumer Politics and the Logic of Early Entrant Protection. Organized disease sufferers and their advocates can bring immense political pressure for approval to bear upon the FDA. Yet the urgency of these appeals is considerably less once an effective drug or two has been approved for a disease. The archetypal case is AIDS (Epstein 1996; Vogel 1990); fundraising for AIDS and political pressure for AIDS drug approvals waned considerably after the approval of azidothymidine (AZT) in 1987. Even though subsequent AIDS treatments were arguably superior to AZT in many respects, they

were not approved as quickly as AZT, at least until 1992. Indeed, as shown in Figure 1, the approval times for AIDS drugs seem to be a roughly increasing function of the order of their approval.

The argument for early entrant protection is a generalization of this logic. Drug approval effectively removes many patients and their advocates (at least partially) from the "political demand pool" for new therapies. We can assume that drug approval dampens political demand for further drugs in rough proportion to the success with which the approved drugs ameliorate or "cure" a disease or a given medical condition. Under most circumstances, when successive drugs for the same disease are roughly comparable in quality, the first few drugs for a disease will have the greatest marginal impact in reducing the size of the political demand pool for new drugs for that disease. The FDA will therefore have reason to give these drugs priority in the approval process and approve them more quickly.

3. Hypotheses and Methods

We seek to test the following claims regarding approval times in FDA drug review.

> **H1 (General Large-Firm Advantage):** Approval times are a decreasing function of the size of the submitting firm.
>
> **H2** (**The Value of Regulatory Familiarity**): Approval times are decreasing functions of the firm's experience in the regulatory process.
>
> **H3** (**Early Entrant Protection, Strong Form**): Approval times are a strictly increasing function of the order of entry.
>
> **H4** (**Early Entrant Protection, Weak Form**): The first drug approved for any given disease receives a quicker approval, ceteris paribus, than subsequently approved drugs.
>
> **H5** (**Interactions between Order of Entry and Political Demand**): Order of entry effects should be an increasing function of the political demand for a drug, or of the political salience of its treatment population.
>
> **H6** (**Capture, Clout**): Approval times are decreasing functions of the political clout of the firm, or of its ability to influence the strategies and votes of politicians and bureaucrats.

To test these claims, we will estimate maximum likelihood duration models of the time to approval. Below we discuss data and measurements for our independent variables of interest. An optimal stopping model of the FDA's problem yields a rather precise prediction about the form of the hazard, namely *non-monotonicity*. The reasoning is rather clear. Given some base of knowledge about the drug at the beginning of NDA review, the marginal value of waiting on the drug (to review or request more information) is highest at the beginning of review. Hence the hazard, or the instantaneous probability of approval given no approval to date, begins at zero and rises. Yet some drugs will never meet the FDA's standards, so the hazard must eventually fall to zero. For simplicity, we choose the log-normal distribution as a functional form for estimation, a form which assumes non-monotonic hazards. We acknowledge that the true distribution is likely more complicated.[3]

A considerable drawback of our approach is our censoring of non-approved drugs. Duration models are usually estimated upon the premise that nothing of significance distinguishes censored observations from terminated ones. The car wreck that kills a patient in the treatment group of lifetime duration analysis, for example, is usually judged to have been an exogenous event, unrelated to the patient's underlying probability of dying. This assumption is certainly violated here. Drugs that are not approved are of less quality than those that are, for one, and many of the factors that affect review times undoubtedly affect the probability of approval in the first place. A potentially superior statistical framework, then, would be a *competing-risks duration analysis*, where the probability of approval conditioned on not yet having terminated due to rejection or withdrawal could be estimated. We are as yet unaware of continuous-time estimators for our problem.[4]

[3] Carpenter (2001) shows that the approval time distribution is a complicated dual mixture of inverse Gaussian forms, one of which is non-defective and one of which is defective.

[4] We note several limitations of our data below, including strategic submissions and the problem of strategic withdrawals by firms. We opt to discuss these drawbacks as data limitation for reasons of clarity, but they also represent weaknesses of our statistical models.

A competing risks framework has one serious hitch, however: the "risks" in FDA drug review are not decisive. The FDA never rejects a drug forever, but instead deems NDAs "not approvable," which means "not approvable *now*." Numerous drugs deemed "not approvable" are soon re-submitted (some immediately) and then later approved. A similar principle holds for firm withdrawals, which are often followed by re-submission. One justification for a censoring approach is that it preserves this uncertainty over non-approved drugs. Theoretically, any non-approved drug still has a positive probability of approval, though one that vanishes as the drug gets older.

4. Data and Measurement

Our data consist of 867 new molecular entities (NMEs) submitted to the FDA over the period 1979 to 2000. Of these 867, 766 have verifiable review time data, and 538 have available firm data such as submission histories, sales and the like. Of the original 867, thirty-seven percent (324) have not yet been approved for some reason (deemed "not approvable" by the FDA, withdrawn by the firm, or still waiting for decision as of September 2000). In the subsamples with review time data and firm data, the proportion of non-approved drugs is 41% and 19%, respectively. In contrast, the FDA reports that approximately 25% of all NDAs are not (eventually) approved (FDA 1988), so our sample may over-sample or under-sample non-approved drugs, depending upon the analysis.[5] All NMEs in our analysis were considered under the FDA's new drug application (NDA) procedures, but not all NDAs during this period are included in our sample. In particular, generic drug applications, supplemental indication submissions which occur when a company seeks to

[5] Acquiring complete data for non-approved drugs is a very difficult undertaking. The essential dilemma is that any and all information concerning an NDA that is not yet approved is considered proprietary under FDA regulations and is excluded from availability under the Freedom of Information Act. In fact, the FDA is legally proscribed from acknowledging the *existence* of a pending NDA until (and only if) the application is approved. We have experimented with weighting our non-approved drugs (see below), and our results do not differ substantively though some of the coefficient magnitudes and standard errors change. In the 1960s, medical reporters reported that approximately "30% of all applications are withdrawn or die as incomplete. Formal rejection is rare." "Safety and skepticism: thalidomide," *Modern Medicine*, October 15, 1962, p. 28.

market its drug for a disease other than the one for which it was originally submitted, and abbreviated new drug applications (ANDAs) are excluded from analysis. Our dependent variable is the review time, in months, from the NDA submission date to the NDA approval date (if approval occurred). Table 1 reports summary statistics of our data.

[Table 1 about here.]

Firm Characteristics. Any number of pharmaceutical firms may combine to develop and market a drug. One firm may discover the chemical entity, license it another for clinical development in return for up-front and "milestone" payments, and then the drug may be marketed by yet a third company. Almost invariably only one of these firms sponsors a new drug application to the FDA. All of our firm-level measures are keyed to the *submitting firm*. In most cases, the submitting firm has played an important role in the clinical development of the drug (funding clinical trials, for example) even if the firm in question did not discover the chemical entity.

Measuring Firm Size. We use several indices to measure the size of firms. We first use world sales in the year of the drug's submission. World sales are preferable to U.S. sales because pharmaceutical revenues can come from a variety of national markets. We calibrate each firm's sales to a common index (U.S. dollars) using average yearly exchange rates, then deflate the dollar aggregates using implicit GDP price deflators. Occasionally, we also use firm-specific employment aggregates, as larger firms will customarily employ more workers. These workers may represent a political constituency – e.g., the "Pill Belt" commonly understood to comprise New Jersey, Eastern Pennsylvania, Delaware and Maryland – that politicians may seek to satisfy by lobbying the FDA.

Measuring Familiarity: Submissions and Mergers. For each drug submitted, we tabulate the number of previous submissions that the submitting firm has *at the date of NDA submission*. Because our sample may not capture all non-approved drugs, our measure probably underrepresents firm submissions. For firms that merged during our sample period, we restart this counter but also code

for the merger with a dummy variable and a separate variable tabulating the years since the firm's most recent merger. Mergers may lead to greater FDA uncertainty over firm attributes; they combine the experience of two or more firms but also generate a "matching" effect about which they agency must learn.

*Measuring Political Clout: Contributions, Domestic Status and Age***.** Large firms are distinguished not only by sales but also by the resources with which to influence politicians and bureaucrats. We expect that this ability will correlate highly with three measures of firm clout: lobbying, age and domestic status.

Our expectation is that larger firms will be more likely to lobby than smaller firms, and that conditional on lobbying, large firms will contribute more than smaller firms. Our data on firms' political contributions come from the Center for Responsive Politics. The recent nature of our data yields a problem, however. Yearly estimates of lobbying activity are unobservable before 1997. Therefore, we use 1997 and 1998 lobbying contributions as measures of political clout throughout the period, dropping firms that died or lost their identity through merger before 1997 when analyzing the effects of lobbying. Still, there are good reasons to use more recent lobbying data. First, pharmaceutical contributions have arisen immensely in the 1990s – particularly with national health insurance and Medicare and Medicaid reform so perennially on the national agenda – which allows us to better distinguish those firms with political resources from those firms without them. Second, our lobbying measures are highly correlated (0.97) from year to year across firms. That is, contributions in 1997 are an excellent predictor of contributions in 1998, 1999 and 2000, and we expect the same for contributions before 1997.[6]

There is a distinct possibility that firm lobbying may be endogenous to regulatory and political outcomes. In particular, firms that do well in the regulatory process may seek to lobby

[6] See www.crp.org, or more recently, www.opensecrets.org.

politicians to maintain this advantage. Yet poor regulatory and political outcomes may also induce firms to lobby more than they otherwise would. For this reason we resort to an instrumentation procedure, described in our results section.

Our second measure We also include a dummy for foreign firms. Foreign firms should ipso facto have less political clout than U.S. firms, as foreign firms are prohibited by law from directly contributing to American campaigns. Moreover, most foreign firms employ a smaller proportion of U.S. citizens than do domestic firms. Olson (1997) finds evidence that foreign firms actually receive quicker approvals on average. At a simple level, Olson's finding is inconsistent with the most basic predictions of capture theory. Our hope here is to test whether Olson's result holds for a larger sample that includes more drugs and a greater span of years.

We also examine the age of the firm, measured as the difference between the year of submission and the year of the firm's founding. Most long surviving firms in the pharmaceutical industry are well-established ones. If the capture theory of regulation is correct, these older firms should have a vested interest in the maintenance of institutions that delay and restrict their competitors' market access.

*Measuring External Signals: Research Specialization***.** Following Olson (1997, 1999), we examine the research and development expenditures of the firm, and we also measure the pharmaceutical specialization of the firm. We first divide the firm's R&D expenditures in the year of a drug's submission by the firm's world sales in the year of submission (adding unity to the denominator, for those cases where sales are zero). To measure pharmaceutical specificity, we divide the firm's total pharmaceutical sales in the year of submission by the corresponding total sales figure (again adding unity). We then multiply each of these fractions by 100 to render the variables in percentage terms.[7]

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[7] We pause to note here that Olson's specialization variables encounter measurement problems when a firm has yet to enjoy any product sales, as is the case with many of the smaller firms in our data set. If R&D is divided by sales for

The Order of Market Entry. Together with pharmacists and public health scholars, we classified the indications for the drugs in our database into over 300 diseases. Then for each drug, we counted the number of drugs previously approved for the drug's primary indication on the date the drug was first submitted.[8] Our variable thus amounts to measuring any drug's "order of entry" into the specific market for a given indication.

Measuring Political Demand for a Drug.[9] Finally, we document the effect of disease politics upon FDA drug approvals by measuring several variables that other scholars have found to be important in the drug approval process (see below for clinical disease characteristics). First, we measure directly the political organization of disease sufferers by using data on disease-specific associations from the Gale Directory of Associations (www.galegroup.com). We first use a simple count of the total number of organizations in the Gale database that include the disease in their title or self-description. We also partial this total into the number of advocacy-related disease-specific groups, the number of research-related groups and the number of support-related groups.

We also use budget- and membership-related measures, such as the aggregate budget and aggregate membership of all groups captured in the tabulations above. We also measure the budget and membership of the largest single organization representing a given disease, as well as the budgets and memberships of the largest five groups representing a disease.[10]

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these firms, the resulting quotient is undefined. We suspect that, because Olson's data set examined only approved drugs, the firms in her sample were larger than the average firm submitting a new drug application to the FDA.

[8] We of course remain responsible for all interpretations and errors in the construction of our dataset.

[9] The effects of the variables described in the next two paragraphs are examined at greater length in Carpenter, "Groups, the Media, and Bureaucratic Delay: Political Influence over FDA Drug Approvals," working manuscript, University of Michigan.

[10] Doubtless our membership variables double count (or treble or quadruple count) individual members, but there may be sound theoretical reasons for doing so. Since highly active individuals in disease politics may belong to more than one group, counting memberships may place extra weight on those diseases characterized by highly committed (perhaps wealthier) activists. In any case, since groups share members but not budgets, our budget variables do not double-count.

We also seek to account for the role of salience that national media give to some diseases. Recent accounts of the FDA have argued that the media has a sizable effect upon FDA behavior. As Herbert Burkholz relates in *The FDA Follies* (1994: 113), "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." In other words, media coverage was a necessary intermediate step for the ability of AIDS groups to place AIDS drugs upon the FDA's priority list. We have tallied the *total coverage* of the disease in the print media (*Washington Post*) and the broadcast media (for the years 1968 to 2000. We use media coverage because it both *reflects* the political organization of a patient group and *boosts* this political influence. The simultaneity here is not troubling for purposes of this paper.[11] Media coverage should reflect the priorities of journalists themselves, politicians and patient advocates. While we hope to untangle these effects with appropriate instrumentation in future analyses, the coverage variable should be correlated with these other indices of the organization and publicity of patient groups.[12]

Controls: Disease Data, FDA Data and Political Oversight. No analysis of FDA drug approval can proceed without attending to the obvious clinical factors at stake. Some diseases are more prevalent and more severe than others. Data on disease prevalence are gathered from the Centers for Disease Control (CDC) and the *Health Yearbook of the United States*. For rare diseases such as Wilson's disease and some forms of skin disease, prevalence and death rate data are difficult to obtain, and these

[11] The effects of the variables described in the next two paragraphs are examined at greater length in Carpenter, "Groups, the Media, and Bureaucratic Delay: Political Influence over FDA Drug Approvals," working manuscript, University of Michigan.

[12] It is extremely unlikely that media coverage of diseases is in any way endogenous to the *timing* of FDA approvals. Most drug approvals are not reported in major newspapers, and those that do usually report them in the business section, as a story about the company receiving approval. In some cases, approval of drugs *may* lead to more awareness of the disease (Prozac and depression, Viagra and erectile dysfunction), but this occurs *after* the drug has already been approved. The measures I employ below use the coverage of the disease *at the time of the drug's submission*, so endogeneity of this sort cannot occur. Finally, the issue in this study is not whether drugs are approved but the *timing* of approval, conditional on being approved. If anything, drugs that are approved more quickly should result in the media having less time to cover them before they are approved.

variables account for most of the missing observations in the estimations of the present study. We gather disease-specific death rates from several sources,[13] and we use this and other information to construct a dummy variable measuring whether or not a disease is a known cause of death.

Consistent with the argument that the FDA values its staff resources more than its fiscal resources (Quirk 1980, Carpenter 1996), we also include the staff level of the drug review division within the FDA – Center for Drug Evaluation and Review (CDER). We also include dummy variables for a Democratic presidency and for Democratic majorities in the House and Senate, as well as "inflation-adjusted" ADA scores for the House and Senate committees that oversee the FDA.[14]

Limitations of the Sample

Before proceeding to analysis, we pause to mention several limitations of the existing sample. The first amounts to a selection problem, though in fact the dynamics are much more complicated than this. We only observe drugs that are submitted to the FDA through the NDA procedures. It is possible (indeed, quite likely) that much of the FDA's influence over firm behavior, and much of large-firm advantage in pharmaceutical regulation, exist at the clinical development stage, when firms decide whether or not to submit a new product in the first place. Clinical trials in drug development are governed by the FDA, which can direct their pace and ask for specific tests. The clinical trial stage (or "IND stage" for "investigational new drugs") has traditionally comprised more than half of the time to market (Dranove and Meltzer 1990).

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[13] Death rate data are from the GMWKI 1997 Death Rate Tables, the report *Morbidity and Mortality: 1998 Chartbook on Cardiovascular, Lung and Blood Diseases* (NIH 1998); the National Center for Health Statistics' *Vital Health Statistics* (different years), and the SEER Cancer Registries.

[14] Congressional oversight becomes more difficult to trace historically for the FDA. In the Senate, the FDA was overseen by the Agriculture Committee to 1954, by the Senate Labor and Public Welfare Committee from 1955 to 1976, and by the Senate Labor and Human Resources Committee from 1977 to the present. The problem comes in determining the relevant House oversight committees. The agency was overseen by the House Agriculture and Forestry Committee to 1940, and its *formal* oversight committee under HEW and HHS has been the Education and Labor Committee.

Because our sample includes only reviewed drugs, it is subject to at least two kinds of error. The first is sample selection bias – we observe higher quality submissions from firms whose cost of rejection is low.[15] The second error (related but not identical) is that, if the FDA induces product abandonment before submission, we may understate large-firm advantage in FDA regulation. (Overstatement of this effect is also possible, but less likely.)

To these objections we can, at present, but plead guilty. Gathering systematic data on all drugs under development over the past 22 years is a monstrous undertaking – as many as 25,000 chemical entities have been developed to some stage of product maturity – which is currently underway. In addition, an explicit formal model of approval decisions with strategic firm submissions would undoubtedly assist this effort, but to our knowledge one has not yet been developed (see Carpenter and Ting 2001 for an early effort).

A second limitation is that we are viewing FDA decisionmaking in a vacuum, while in fact the FDA is perpetually involved in a massive, multi-country waiting game with other regulators such as Britain's Medicines Control Agency (MCA). This pattern may induce spurious results in our regressions because the FDA may take cues from other nations' approvals. If, for example, some of our exogenous variables influence UK or EU approvals, but influence US approvals only through FDA cueing upon the decisions of other regulators, then our results may be spurious. We discuss this interpretation of several of our findings below. A multi-national, multi-regulator study of drug approvals is also a future aim of our research.

5. Empirical Analysis

We seek first to document whether large-firm advantage really prevails in pharmaceutical regulation. We rely throughout upon firm sales as the crucial measure here. Figure 2 shows non-parametric (Kaplan-Meier) estimates of the survivor function of firms, stratified by six categories of

[15] Either the firms' cost of rejection is low relative to other *firms*, or the cost of rejection is low relative to other *times* for

firm sales. With several exceptions, NDAs submitted by larger firms receive approval more quickly than NDAs submitted by smaller ones. At 15 months of review time, for example, over 40% of NDAs submitted by firms in the largest sales category (above $13.4 billion) have been approved, whereas only 15% of NDAs submitted by "small" firms have been approved by that time. Indeed, for our sample, approximately one in four drugs submitted by these "small" firms *never* get approved.

[Figure 2 about here.]

We turn next to maximum likelihood estimation with covariates. Table 2 reports log-normal duration models with sales, firm submissions and merger effects as covariates in five different models. Table 3 reports the marginal effects estimates from the models in Table 2. The first two columns of results compare the effect of firm size under two different samples: one in which non-approved drugs are excluded [model (1)] and one in which they are included [model (2)].

[Tables 2 and 3 about here.]

The results show that estimated large-firm advantage is considerably suppressed when the sample excludes non-approved drugs. The coefficient on sales approximately doubles, from –0.0350 to –0.0678, when non-approved drugs are added to the sample. Because marginal effects of a variable are not a linear function of the estimated coefficient, moreover, the marginal effects more than double. Adding non-approved drugs to the sample increases the estimated marginal effect of firm sales upon duration by over 250%. At the mean of the sales variable – ln(*Sales*) equals 7.66, or *Sales* equals $2.1 billion – a one-unit increase in logged sales (to $5.8 billion) is associated with a two-month reduction in review time. Going from the minimum to maximum of logged sales (zero to 10.68, or about $43 billion) is sufficient to generate a *two-year expected differential* in review time for the

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the same firm. Similar errors result in either case.

larger firm. Clearly there is an effect of size, one that is vastly underestimated by samples restricted to approved products.[16]

[Figure 2 about here.]

The remaining models in Tables 2 and 3 offer simple tests of the familiarity hypothesis. Model (3) shows that when firm submissions are added to equation (2), the estimated effect of firm size drops by 31% in coefficient value, and by 29% in its marginal effects. Generally, firms with more submissions receive shorter review time, an effect that is robust across repeated estimations of the log-normal review duration models. From the estimates of model (3), a standard deviation increase across firms in number of previous submissions (6.15) is associated with a three-month reduction in expected FDA approval time. Moving from the minimum (1) to the maximum (30) of this variable is sufficient to generate an expected advantage in approval time of 15 to 18 months, depending on the particular marginal effects estimate retrieved from Table 3. We offer a plot of average review times for firms at different levels of the submission variable in Figure 2. The trend is downward and generally linear. Almost one-third of large-firm advantage in these simple models, then, can be explained by reference to the greater regulator familiarity that large firms enjoy.

[Figure 3 about here.]

Models (4) and (5) of Tables 2 and 3 report the additional effects of mergers and the interaction of mergers and submission histories. Merged firms (which submitted only eight percent of the drugs in our sample) enjoy a seven-month reduction in expected approval time. Adding either the merger dummy variable alone or an interaction term multiplying submissions times the merger dummy is sufficient to reduce the sales coefficient by 46 to 55 percent. The impact upon the

[16] A linear specification of large-firm advantage (using non-logged sales instead of logged sales in the model) yields a negative but statistically negligible coefficient (β = -2.67E-06; SE = 1.79E-06). A model with non-logged sales produces a log-likelihood of –501.082 and likelihood ratio of 2.23 (Pr = 0.1354), while the model with logged sales yields –493.036 and a likelihood ratio of 18.32 [Pr = 0.000]. In other words, logged sales is clearly a superior specification to non-logged sales. The intuitive inference from this result is that whatever advantages large-firms enjoy in pharmaceutical regulation are characterized by decreasing marginal returns to size.

marginal effect of firm sales is more drastic. The marginal effect of logged sales drops by 60 percent from model (2) to model (5), while the elasticity drops by 58 percent.

Why do merged firms do better? Familiarity is undoubtedly one important mechanism. Model (5) of Tables 2 and 3 shows that the effect of firm submissions is greater for merged firms. Two effects merit remark. First, firm mergers often combine the reputations of two well-established companies into one. Second, mergers create a "matching effect" between two firms which may initially give the FDA *greater* uncertainty, not less. If the agency was relatively sure about quality control at Glaxo and Wellcome, it may be less sure about quality control at Glaxo Wellcome. It is for this reason that the effect of firm submissions is greater for merged firms; a merger forfeits some degree of familiarity, at least initially.

[Table 4 about here.]

How stable is large-firm advantage generally, and the advantage of familiarity more specifically? Table 4 offers a set of duration regressions stratified by thirteen disease categories (comprising 83.1% of the sample), by lethality of disease and by time, specifically before and after the most important regulatory innovation of this period, the Prescription Drug User Fee Act (PDUFA) of 1992. With three exceptions – mental health, OB/GYN and imaging drugs – the sales coefficient estimates negative across the disease-based subsamples. The effect is most pronounced in pulmonary-respiratory and anti-viral/anti-infective and dermatological drugs, and is rather small for cancer and cardiovascular drugs. Size advantages are much more pronounced for products for lethal diseases than for non-lethal ones, and are almost identical for samples before and after 1992.

A negative relationship is observed between submissions and review time in nine of the thirteen disease subsamples, the "exceptions" all emerging in disease categories that contribute fewer drugs to the sample. The most pronounced effects emerge in products for pulmonary-respiratory,

muscular-skeletal, cardiovascular, urological, anti-infective/anti-viral and dermatological conditions. Crude lethality of disease does not affect familiarity advantages, but the estimated coefficient on submissions drops by half (though remains statistically significant) after PDUFA.[17]

Table 4, then, supports the relative stability of size and familiarity advantages across disease categories. It also shows, in the rightmost column of estimates, that controlling for submissions drastically reduces the effect of sales in almost all disease categories, across lethality. In the post-PDUFA sample, however, the sales variable retains a significant effect even when firms and mergers are included in estimation.

[Table 5 about here.]

Order of Entry, Foreign Status and Age. We now present, in Table 5, a more general set of models without disease-specific information. The first two models estimate NDA approval times as a function of logged firm sales, firm submissions, the merger-submissions interaction, a dummy variable for orphan drug status, the order of entry, and a dummy variable for whether the firm is headquartered in a foreign country. Model (1) excludes the disease categories of Table 4, while model (2) includes them. Models (3) and (4) add age of the submitting firm, and exclude and include disease categories, respectively. As in previous estimations, logged sales and submissions estimate consistently negative, and in particular the estimated effect of both variables (especially sales) grows as more variables are added. Orphan drugs consistently receive shorter approval times than do non-orphan drugs, although this effect does not remain statistically significant throughout estimation. (We discuss other "priority" categories for drugs below.)

Order of entry effects estimate consistently positive across samples that exclude disease categories, but consistently insignificant across samples that include these dummy variables. In the

[17] Olson (2000) suggests that the incentive provisions of PDUFA removed FDA incentives to process "signals" based upon firm information. We do not test this claim here.

models (1) and (3) the associated marginal effect of the order of entry variable is 0.2024 months in expected review time. Submitting the tenth drug for a given disease as opposed to submitting first accounts for an average delay of two months. Moving from the minimum (1) to the maximum (55) of this variable yields an expected additional year of approval time. Why do entry-order effects disappear when disease categories are included? The reasons are probably twofold. First, these categories are blunt and subsume many fine-grained medical indications. "Anti-infective" drugs, for instance, treat everything from pneumonia to Lyme's disease and head lice, while "urological" drugs treat gallstones and erectile dysfunction. Second, the order-of-entry effects probably have their greatest effect upon FDA-wide decision making, that is, *across* disease categories. It is not merely the case that the second drug for angina will have a lower expected approval time than the seventh, but that the second drug for angina will get approved more quickly than the seventh for urinary tract infections. We will see additional evidence for this proposition in our analysis of priority ratings.

The two surprises of Table 5 come in the apparent advantages of foreign firms and the disadvantage of older firms. Marginal effects from calculations in Table 6 show that foreign firms have on average a two-month advantage in approval time for every drug they submit. This advantage shrinks in magnitude across the estimations in Table 5 but retains its sign. The coefficient on firm age, likewise, is positive, suggesting that older firms do *worse* in the FDA review process than do younger ones. Using marginal-effects calculations from Table 6, a standard-deviation increase in firm age at submission (51.3) years is associated with a rise of 3 months in expected approval time.

We do not unpack these results here,[18] except to offer a rather straightforward inference. They are both rather inconsistent with the predictions of capture theory. Rent-seeking would predict that domestic firms will be privileged over foreign ones, at the very least not disadvantaged

[18] Olson (1997) also finds a foreign firm advantage in her samples, and surmises that foreign firms may simply enjoy a quality advantage, though she does not directly test this claim.

relative to foreign firms. One would particularly expect this pattern in U.S. pharmaceutical regulation, given the FDA's long history of being more danger-averse than regulators overseas (Grabowski and Vernon 1983) and the cohesive political organization of pharmaceutical manufacturers here. The estimated coefficient on our firm age variable suggests that long membership and standing in "the industry" means little unless the firm has large sales and is well-known to the regulator.

In the interest of proper controls, Table 5 also includes covariates measuring the partisan majority in the House and Senate, the median ideology score of the FDA's House and Senate oversight committees, and the partisanship of the president. Across all of my estimations, in any combination, all five of these variables fail to attain standard levels of statistical significance.

[Table 6 about here.]

The Effect of Disease Politics. In Table 6, we add to our estimations a set of variables measured at the disease level. Model (1) includes a lethal disease dummy variable, and mid-1990s estimates of the death rate and the prevalence of the condition which represents the primary indication of the NDA. The first result to which we draw attention is that our sample size falls by approximately 35% from the estimations of Table 5. It is simply very difficult to acquire comparable information on incidence and death rates for over 300 diseases. We present the following results with caution.

Model (1) of Table 5 shows that neither the lethality, nor the death rate nor the prevalence of the primary indication for a drug has an effect upon FDA review times for that drug. Models (2) and (3) add variables measuring the "political demand" for drug approval. These include our group aggregate measure, the budget of the disease organization with the largest budget, and our measure of media attention to the disease, typically a moving average of mentions in the *Washington Post* for the four years preceding and including the year of submission. (In separate estimations the Vanderbilt TV news measure always estimates with less force than the *Post* measure.)

Across these estimations the most consistent effects are observed from the maximum budget variable and the *Post* coverage variable. Both are negatively associated with review times, as expected, but the maximum budget is negatively associated with review times only when it is interacted with the order of entry variable. The proper interpretation is that a well-funded "peak" organization for a medical condition is associated with reduced NDA review times for drugs for that condition only when the order of entry is high. Groups such as the American Heart Association have their greatest impact upon FDA approval then, not when the first drug for ventricular tachycardia appears, but when the twentieth entrant for hypertension is submitted.

The public salience of the disease also matters. Controlling for two measures of severity and for prevalence, and for two measures of disease advocacy, media coverage of a disease *before* drug submission is associated with reduced review times across numerous estimations. Estimated marginal effects from Table 6 suggest that a one-standard-deviation increase in non-obituary *Washington Post* stories mentioning a medical condition (289 stories) is associated with an 8.7-month reduction in NDA approval time.

How does "political demand" for approvals influence large-firm advantage in the FDA review process? Adding these five variables – the group aggregate, the budget aggregate, interactions of both of these variables with order of entry, and the Post coverage variable – reduces the estimated effect of firm sales upon review times by an additional 21 percent, and by over 25 percent in marginal effects. Our inference is that "disease politics" probably works to the marginal advantage of large firms. Large firms are, for one, better able to target drugs to politically organized and publicly salient disease populations. They may be better able to ally with large peak associations and disease advocacy organizations to pressure the FDA for priority ratings, or for orphan drug status for some diseases. They may also be able to create "front" consumer organizations to pressure Congress and the FDA to quicken drug approval, and to generate more media coverage for

their causes.[19] We note, to conclude discussion of Table 6, that the effect of submissions, order of entry, firm age and CDER staff remain statistically significant across the estimations there.

[Table 7 about here.]

An Analysis of Priority Ratings

Readers might wonder why we have not included FDA "priority" ratings in the estimations of Tables 2 through 6. Our reasoning is that priority ratings are entirely endogenous to the political and organizational factors we have identified. Firms and disease advocates commonly lobby for priority ratings for their drugs, and priority ratings also reflect FDA judgments about product quality or risk, judgments affected by firm reputations. To be sure, priority ratings are undoubtedly driven by clinical considerations, but we remain confident that they are also influenced by political ones.

There is a crucial didactic reason for analyzing priority ratings, however. They are established before NDA review and remained fixed over the entire review. Any factor affecting FDA priority ratings therefore exercises its influence *before* the FDA commences drug review. We can, therefore, ascertain something about the causal mechanism of regulatory advantage by examining priority ratings, which we do in Table 7. Table 7 reports probit regressions in which drugs that receive the highest priority ratings of the various classifications over the past twenty years are scored 1, and are scored 0 otherwise.

Table 7 shows that large firms are no more likely to receive priority ratings than smaller firms are. Indeed, the estimated coefficient on logged sales is *negative*. Whatever advantages large firms may have in FDA regulation, they are not more likely to receive priority ratings for their drugs. Firms with more submissions are, however, more likely to receive priority ratings, which suggests that these ratings are probably a function of agency judgments about likely product quality and

[19] The paucity of data on this observation prevents us from examining this hypothesis in greater detail, but we note that business-funded disease advocacy organizations are a very recent phenomenon, one that affects the last five years of our data at most.

safety, uncertainty over which is reduced by solid firm reputations. For this reason, firms created by merger are, in models 2 and 3, statistically more likely to receive priority status for their drug submissions.

Other influences are rather straightforward. Later entrants to a disease-specific market are less likely to receive priority status, while orphan drugs are more likely to receive it. The estimations also show the effect of FDA operational variables and disease politics, as priority ratings are more likely when a disease has a well-heeled peak association, and have become more common with increasing CDER staff size.

The Effect of Lobbying

We conclude our estimations by turning to a final test of rent-seeking theory. Table 8 reports NDA duration estimations in which all models include firm lobbying itself or an instrument for firm lobbying. We instrument for lobbying, again, because it may be driven by good or bad outcomes in the regulatory process. Identifying a plausibly exogenous covariate of lobbying that is not also a covariate of regulatory success is difficult. We offer only a few plausible candidates here.

Our instruments are chosen according to the following logic. Firms are more likely to lobby when more interests (shareholders, cooperating firms) are potentially affected by their regulatory outcomes. If these interests are concentrated, they are more likely to benefit from rent-seeking by the firm. It is for this reason that we choose public ownership and ownership concentration as plausible instruments for lobbying. Publicly owned firms must be more responsive to a broader array of stockholders than privately held firms are. The advantages of rent-seeking, if any, will more immediately benefit the firm's managers if the firm is public. Using information from SCRIPS Reports, we also code a variable representing whether more than 5 percent of the firm is owned by a

single shareholder, and where this variable is coded 1, we code for the total percentage of firm owned by the top shareholder.

Our second set of instruments measures the propensity of a firm to strike agreements with other firms to develop drugs. Compiling information from SCRIPS Reports on annual agreements in the 1990s, we regressed a ten-year average of agreements upon two different sets of independent variables: firm sales (larger firms are more likely to strike agreements), merged firms, foreign firms, firm employment, and firm age in one of the two models. (These variables together explained 53 or 54 percent of the variation in agreement propensities across 125 firms.) We then retrieved the residuals from this regression and used them to instrument for lobbying.

Our final instrument concerns the composition of a company's pipeline. We code, for the mid-1990s, the proportion of a firm's drugs under development that are at each of three stages: (1) preclinical, (2) clinical testing but pre-NDA, and (3) under NDA review. We take the first of these proportions and use it to predict lobbying. Our reasoning is that firms in fact rarely contribute money to influence quick FDA approvals. Usually they have done their political homework long before the NDA review stage, and in fact most pharmaceutical lobbying does not concern issues of NDA review. Instead, pharmaceutical firms usually lobby for targeted NIH funding, for changes in clinical regulations, for an enhanced climate of development. All of these incentives to lobby are likely to be correlated with the "early" proportion of a firm's pipeline, and this variable seems rather random across firms.

Do these instruments affect drug approval in ways other than through the lobbying mechanism? Skeptically, one can conjure up endogeneity concerns for all four. By virtue of being publicly traded, public firms may be able to signal the FDA about the quality of a drug through investor reports, stock prices and the like. Firms that strike many agreements may do so because others are willing to enter into agreements with *them*, precisely (that is) because of their reputation.

A large number of drugs early in the pipeline at a given time may signal the FDA about the current research intensity of the firm. Concentrated ownership may itself reflect the signal of a single shareholder whose continuing vestment speaks to the firm's underlying value.

Mindful of these drawbacks, we proceed to estimate the effect of firm contributions upon NDA approval times in Table 8. Predicted value of lobbying were generated using either OLS or a tobit regression,[20] and the first three columns of estimates report the coefficient on this variable for models of varying complexity. The first instrument, public ownership, offers a surprise. Publicly-owned firms are indeed more likely to lobby than private ones, but in fact this instrument contributes to *longer* review times not shorter ones. It is possible that public ownership slows drug review because publicly owned firms may wish to optimally time good news from the FDA (or delay bad news); hence publicly-traded firms may request slower FDA approvals.

The other estimations show that instrumented lobbying is negatively associated with NDA review times for the concentration and pipeline instruments. The agreement instrument produces statistically insignificant estimates of the effect of lobbying. Once the submissions variable alone is added to the model, however, no lobbying variable, instrumented or not, estimates non-zero. In more robust statistical models adding variables in Table 4, only the pipeline tobit lobbying instrument is significantly negatively associated with NDA review times. By contrast, the firm submissions variable is negative and remarkably consistent across these various estimations.

Alternative Explanations

Have We Found Greater Regulatory Familiarity with the Firm, or Greater Firm Familiarity with the Regulator? The insignificance of the age coefficient suggests that regulatory familiarity is the better

[20] More appropriate statistical estimators for predicting contributions doubtless exist. Given the complexity of our second-stage estimation problem, however, we have decided to keep our instrumenting regressions as simple as possible. We have also left unadjusted the standard errors in Table 8 estimations. A consistent estimator of the asymptotic covariance matrix (e.g., a Murphy-Topel correction) would add a positive-definite increment to the estimated matrix, and the asymptotic standard errors would be at least as large as those reported in Table 8.

option, though this is not definitive. The enhanced effect of mergers upon submissions also suggests FDA learning rather than firm learning. When large firms merge, there is little if any new learning to be done about the FDA by these giants. The firms usually retain a core set of personnel devoted to regulatory affairs. It is the *FDA* that confronts uncertainty about a newly merged firm, not vice versa. A genuine test would be to ascertain whether the submission effect varies with FDA operations variables that might affect organizational learning, such as turnover.

Does the Number of Previous Approvals for a Disease, Firm Submissions or Sales Proxy for the Passage of Time? If so, the effect for order-of-entry should be the opposite of what is observed, as FDA drug approvals have been getting quicker, not slower, over the past twenty years. As for submissions and sales, these effects do not vanish when we control for the year of submission or for CDER staff, which increases over the course of data set and is the best candidate for explaining the reduction in drug review time in the last 15 years.

Do Firms with More Submissions (and More Approvals) Have a Greater Vested Interest in Slowing the Entry of Competition? We have considered this, but doubt it. For one, vested interest in slowing market entry would be more likely a function of sales. For another, if we examine changes in lobbying during the 1990s (a decade during which thousands of new pharmaceutical products were developed), they are negatively correlated with firm submissions, though not heavily so. In other words, just as all sorts of threats to established firms have been emerging in the regulatory process, firms with more drugs have been lobbying less, not more.

6. Conclusion: Implications and Alternative Explanations

A large-scale analysis of NDA review times for new molecular entities developed over the past 22 years reveals that large-firm advantage in FDA regulation is real and tangible. Indeed, scholars restricting their analyses to approved drugs have been less likely to find it. Our analysis

shows that inclusion of non-approved drugs increases the estimated effect of firm size upon NDA approval times by as much as 250 percent. Clearly, size matters in FDA drug regulation.

Yet when we turn to explain large-firm advantage at the FDA, our results are remarkably inconsistent with the most basic predictions of rent-seeking theory. Domestic firms do much worse than foreign firms in FDA regulation, and older firms do worse than younger ones. Analyses of lobbying contributions, moreover, show inconsistent results that disappear once other covariates are added to estimation.

Our analyses show that, once the effect of mergers is accounted for, the simple advantage of being better known to the agency accounts for as much as 55% of estimated large-firm advantage in NDA approval times. Another 15-20% of that advantage can be accounted for by what we call *disease politics*, the variable organization of disease sufferers and their advocates, and the differential attention that media organizations give to some medical conditions over others.

We conclude by acknowledging the very real possibility that capture and rent-seeking may express themselves in other venues, namely the ability of the FDA to induce pre-NDA product abandonment through rulemaking and expectations of delay at the NDA review stage. These hypotheses remain untested, and the proper framework for doing so remains one which submissions are endogenous to the review process, both theoretically (Carpenter and Ting 2001) and empirically, through joint estimation of a submission equation and an approval equation. The present paper, we hope, has clarified what the sample ought to look like (it need include non-approved drugs), has elucidated the importance of firm reputations and disease politics, and has clarified the behavior of the FDA, the last mover in the complicated game of drug development.

Table 1:
Descriptive Statistics for Selected Variables

VARIABLE	Valid N	Mean (Std Error)	Min	Max
Approval Time (in months) for approved NMEs	446 drugs	24.64 (19.16)	0.59	122.49
Review Time (in months) for all NMEs	766 drugs	42.16 (50.66)	0	221.06
World Sales of Firm (yr of submission) [in millions of 1990 U.S. $]	459 drugs	8458.196 (21482.46)	0	43479.000
Number of Submissions of Submitting Firm (at date of submission)	538 drugs	6.60 (6.15)	1	30
Age (in years) of Submitting Firm (year of submission)	481 drugs	66.25 (51.31)	0	325
Merger Dummy (=1 if created by merger)	203 firms	0.08 (0.27)	0	1
Foreign Firm (=1)	193 firms	0.39 (0.49)	0	1
Publicly Owned (=1)	202 firms	0.85 (0.36)	0	1
Total Firm Contributions, 1998 (millions of U.S. dollars)	210 firms	0.200 (0.829)	0	8.0
Order of Approval of a Drug for Indicated Disease, 1979-2000 [= # drugs previously approved for disease – 1]	699 drugs	9.38 (10.77)	1	54
Dummy: Is primary indication of drug a lethal disease?	173 diseases	0.43 (0.50)	0	1
Average 1990s Prevalence of Indication Disease [per 10,000 U.S. inhabitants]	127 diseases	36.30 (79.83)	0	448.55
Average Death Rate of Indication Disease [per 10,000 U.S. inhabitants]	97 diseases	0.07 (0.31)	0	2.78
Number of Non-Obituary Stories Mentioning Indication Disease in *Washington Post*, 1995	286 diseases	69.54 (601.74)	0	2948
Number of Nightly News Stories Mentioning Disease, 1995 [Vanderbilt TV News Archive]	153 diseases	1.98 (9.83)	0	114
Four-year average mentions of indication disease in *Washington Post*, up to and including submission year	503 drugs	101.7 (289.9)	0	3115
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	205 diseases	$2.86M ($8.60M)	$0	$80.4M
Dummy: Orphan Drug [=1]	745 drugs	0.10 (0.30)	0	1

Table 2: Effect of Firm Sales upon Approval Times, NCEs Approved 1979-2000

[Maximum likelihood estimates based upon the lognormal duration distribution.]

	(1)	(2)	(3)	(4)	(5)
Constant	**3.1710** (0.1397)	**3.5620** (0.1317)	**3.5284** (0.1309)	**3.4681** (0.1311)	**3.4695** (0.1372)
ln(Sales)	**-0.0350** (0.0167)	**-0.0678** (0.0159)	**-0.0470** (0.0178)	-0.0300 (0.0183)	**-0.0368** (0.0186)
Firm Submissions	-----	-----	**-0.0179** (0.0072)	**-0.0202** (0.0071)	**-0.0156** (0.0072)
Merger Dummy	-----	-----	-----	**-0.2883** (0.0966)	-----
Merger Dummy × Firm Submissions	-----	-----	-----	-----	**-0.0274** (0.0107)
σ	0.7332 (0.0269)	0.8047 (0.0295)	0.7972 (0.0292)	0.7810 (0.0287)	0.7920 (0.0295)
Non-approved drugs included?	No	Yes	Yes	Yes	Yes
N (df) LLF	372 (369) -417.635	459 (456) -493.036	459 (455) -489.986	459 (454) -474.262	457 (454) -475.096

Table 3: Marginal Effects and Elasticities on Approval Time for Sales, Submissions and Mergers

[Maximum likelihood estimates based upon the lognormal duration distribution.]

	Effects	(1)	(2)	(3)	(4)	(5)
ln(Sales) [Std Dev = 2.75]	dy/dx *Elast.*	**-0.8048** ***-0.2753***	**-2.0220** ***-0.5314***	**-1.4247** ***-0.3774***	**-0.9168** ***-0.2504***	-0.8088 *-0.2238*
Firm Submissions [Std Dev = 6.15]	dy/dx *Elast.*	-----	-----	**-0.4995** ***-0.1239***	**-0.5494** ***-0.1404***	**-0.6147** ***-0.1616***
Merger Dummy [Std Dev = 0.27]	dy/dx *Elast.*	-----	-----	-----	**-7.3489** ***-0.0644***	-----
Merger Dummy × Firm Submissions	dy/dx *Elast.*	-----	-----	-----	-----	**-0.9096** ***-0.0549***
Mean of Approval Time		23.59 months	29.10 months	28.9 months	28.13 months	28.7 months
Non-approved drugs included?		No	Yes	Yes	Yes	Yes

Note: Marginal effects and elasticities are calculated at means of independent variables.

Table 4: Size and Familiarity Effects,
Stratified by Disease Category, Lethality, and Regime

[Maximum likelihood estimates based upon the log-normal duration distribution.]

VARIABLE	% of Sample in Category	β_{sales} [model includes sales variable only]	$\beta_{submits}$ [model includes submissions variable only]	β_{sales} [model includes submissions & merger variables]
Muscular-Skeletal	8.9	**-**0.0963 (0.0750)	**-0.0486** (0.0161)	-0.0269 (0.0712)
Pulmonary-Respiratory	4.4	**-0.4924** (0.1218)	**-0.0712** (0.0218)	**-**0.4678 (0.3269)
Cancer	9.7	**-0.0625** (0.0420)	-0.0270 (0.0205)	-0.0397 (0.0462)
Endocrine	3.2	**-0.0478** (0.0253)	-0.0033 (0.0204)	-0.0660 (0.0458)
Cardiovascular	18.0	**-**0.0550 (0.0560)	**-0.0239** (0.0116)	-0.0084 (0.0582)
Urology-Kidney	1.8	**-**0.0461 (0.0718)	**-0.0432** (0.0188)	0.0668 (0.1198)
Mental Health	5.6	0.0575 (0.1477)	0.0317 (0.0403)	0.0978 (0.1689)
Infectious/Viral	16.2	**-0.1653** (0.0543)	**-0.0502** (0.0167)	-0.0880 (0.0539)
Obstetric-Gynecological	1.4	0.2773 (0.4181)	0.0101 (0.0105)	0.1959 (0.4847)
Dermatological	3.0	**-0.1966** (0.0858)	**-0.0697** (0.0343)	**-0.2649** (0.1200)
Gastrointestinal	2.6	**-0.1168** (0.0678)	**-0.0049** (0.0185)	**-0.1193** (0.0694)
Neurological	4.5	-0.0371 (0.0431)	0.0185 (0.0165)	-0.0326 (0.0443)
Imaging	3.8	0.0093 (0.0704)	0.0623 (0.0892)	0.0511 (0.0616)
Lethal Disease	52.5%	**-0.0949** (0.0353)	**-0.0324** (0.0117)	**-**0.0187 (0.0329)
Non-lethal Disease	47.4	-0.0599 (0.0366)	**-0.0266** (0.0092)	-0.0261 (0.0436)
Pre-PDUFA	63.2%	**-0.0742** (0.0284)	**-0.0318** (0.0105)	-0.0273 (0.0318)
Post-PDUFA	36.8	**-0.0692** (0.0168)	**-0.0146** (0.0066)	**-0.0646** (0.0206)

Note: Number of NDAs = 772. Therapeutic categories for pediatric, otolaryngology, ophthalmology excluded.

Table 5: Duration Analyses of NCEs Reviewed 1979-2000, Firm-Level and Entry-Order Effects

[Maximum likelihood estimates based upon the lognormal duration distribution.]

Variable	(1)	(2)	(3)	(4)	(5)
Constant	**3.5747** (0.1626)	**3.2700** (0.1775)	**3.4896** (0.1678)	**3.2361** (0.1798)	**3.9913** (0.9243)
Ln(Sales)	-0.0328 (0.0210)	**-0.0395** (0.0204)	**-0.0523** (0.0227)	**-0.0640** (0.0219)	**-0.0759** (0.0199)
Firm Submissions	**-0.0219** (0.0077)	**-0.0219** (0.0073)	**-0.0250** (0.0080)	**-0.0258** (0.0076)	**-0.0150** (0.0070)
Firm Submissions × Merger	**-0.0197** (0.0114)	-0.0100 (0.0111)	-0.0086 (0.0123)	0.0035 (0.0119)	0.0167 (0.0110)
Orphan Drug Dummy	**-0.2117** (0.1207)	-0.1530 (0.1187)	-0.1961 (0.1240)	-0.1406 (0.1207)	**-0.2078** (0.1097)
Order of Entry (Disease)	**0.0078** (0.0038)	-0.0002 (0.0046)	**0.0074** (0.0040)	-0.0007 (0.0047)	0.0041 (0.0043)
Foreign Firm	**-0.2342** (0.0907)	**-0.2029** (0.0872)	**-0.1999** (0.0947)	**-0.1549** (0.0905)	-0.0949 (0.0828)
Age of Firm (years) at Submission Date	-------	-------	**0.0024** (0.0010)	**0.0029** (0.0009)	**0.0015** (0.0009)
Democratic President	-------	-------	-------	-------	0.1475 (0.2569)
Democratic Senate Majority	-------	-------	-------	-------	-0.4695 (0.4901)
Democratic House Majority	-------	-------	-------	-------	-0.0359 (0.8668)
Median ADA Score, Senate Committee	-------	-------	-------	-------	-0.3406 (1.7945)
Median ADA Score, House Committee	-------	-------	-------	-------	-1.8444 (1.9384)
CDER Staff	-------	-------	-------	-------	-0.0004 (0.0005)
σ	0.7467 (0.0444)	0.6958 (0.0414)	0.7522 (0.0467)	0.6924 (0.0431)	0.6330 (0.0374)
$\ln(\theta)$ [Inverse Gaussian Frailty Parameter]	-2.4111 (1.1069)	-2.1167 (0.8663)	-2.3596 (1.1275)	-1.9970 (0.8382)	-2.1107 (0.8571)
Disease Category Dummy Variables?	No	Yes	No	Yes	Yes
N (N approved)	427 (348)	427 (348)	410 (332)	410 (332)	410 (332)
LLF	-451.797	-431.455	-436.055	-413.622	-385.872

Table 6: Log-Normal Duration Analyses of NCEs Reviewed 1979-2000, Adding Disease-Level Effects				
Variable	(1)	(2)	(3)	**Marginal Effects** [dy/dx, then elasticity (italicized)]
Constant	**5.3515** (0.4034)	**4.8760** (0.4748)	**4.3442** (0.5503)	
Ln(Sales)	**-0.0581** (0.0301)	-0.0464 (0.0329)	-0.0338 (0.0334)	-0.6957 *-0.2297*
Firm Submissions	**-0.0215** (0.0096)	**-0.0170** (0.0103)	**-0.0233** (0.0108)	**-0.4703** ***-0.1443***
Firm Submissions × Merger	0.0120 (0.0145)	0.0082 (0.0166)	0.0046 (0.0165)	0.0180 *0.0141*
Orphan Drug Dummy	**-0.2353** (0.1578)	-0.1486 (0.1649)	-0.1534 (0.1637)	-3.3288 *-0.0215*
Order of Entry (Disease)	0.0072 (0.0048)	**0.0658** (0.0245)	**0.0642** (0.0244)	**1.2553** ***0.5680***
Foreign Firm	-0.0735 (0.1154)	-0.0797 (0.1274)	-0.1042 (0.1275)	-3.4754 *-0.0672*
Age of Firm (years) at Submission Date	**0.0026** (0.0013)	**0.0025** (0.0014)	**0.0028** (0.0014)	**0.0623** ***0.1315***
Lethal Disease (Primary Indication)	-0.0400 (0.1209)	-0.0364 (0.1561)	-0.0574 (0.1553)	-2.1098 -0.0856
Death Rate (Primary Indication)	-0.0834 (0.1928)	-0.0849 (0.1978)	-0.1162 (0.1968)	-0.0037 *-0.0121*
Prevalence (Primary Indication)	0.0004 (0.0004)	**0.0026** (0.0009)	**0.0025** (0.0009)	**0.0522** ***0.3057***
CDER Staff	**-0.0014** (0.0002)	**-0.0013** (0.0003)	**-0.0012** (0.0003)	**-0.0318** ***-1.8448***
Total Groups (Primary Indication)	-------	0.0043 (0.0029)	0.0040 (0.0029)	0.1100 0.1096
Groups × Order of Entry	-------	-0.0007 (0.0008)	-0.0005 (0.0008)	-0.0093 -0.0004
Budget ($10M) of Group with Largest Budget	-------	0.0143 (0.0114)	0.0125 (0.0114)	0.1930 *0.0829*
Budget × Order of Entry	-------	**-0.0023** (0.0010)	**-0.0023** (0.0010)	**-0.0405** ***-0.3427***
4-yr Average of Disease Coverage in *Post*	-------	**-0.0014** (0.0005)	**-0.0014** (0.0004)	**-0.0301** ***-0.1245***
Democratic President	-------	-------	0.0208 (0.2101)	0.5029 0.0106
Democratic House Majority	-------	-------	0.1153 (0.1883)	2.7619 0.0693
Publicly Owned Firm	-------	-------	0.3463 (0.2178)	7.2466 *0.3247*
σ	0.7292 (0.0367)	0.6819 (0.0396)	0.6760 (0.0392)	Predicted Mean of Approval Time: 24.2 months
N (N approved)	247 (204)	184 (153)	184 (153)	
LLF	-256.058	-179.950	-178.170	
Note: Standard errors in parentheses; significant coefficient estimates (and marginal effects, elasticities) in bold. Disease categories excluded.				

Table 7: Probit Analyses of NCE Priority Ratings

[Dependent Variable scored 1 if drug received "1A," "1AA," or "1P" rating, 0 otherwise.]

Variable	(1)	(2)	(3)	(4)
Constant	**-0.3925** (0.1906)	**-1.1288** (0.5349)	-0.9488 (0.6503)	**-4.0086** (1.5212)
Ln(Sales)	-0.0299 (0.0269)	-0.0192 (0.0473)	-0.0771 (0.0610)	-0.0366 (0.0700)
Firm Submissions	**0.0339** (0.0116)	**0.0384** (0.0166)	**0.0433** (0.0202)	**0.0450** (0.0219)
Order of Entry (Disease)	**-0.0208** (0.0072)	**-0.0245** (0.0076)	**-0.0404** (0.0109)	**-0.0857** (0.0493)
Orphan Dummy	-------	**1.2716** (0.2525)	**0.8860** (0.2935)	**1.0508** (0.3190)
Merger Dummy	-------	0.3053 (0.2265)	**0.5993** (0.2700)	**0.5458** (0.3151)
Foreign Firm	-------	0.1827 (0.1805)	0.2533 (0.2159)	0.0337 (0.2333)
Age of Firm (years) at Submission Date	-------	-0.0006 (0.0022)	0.0015 (0.0025)	0.0007 (0.0026)
Publicly Owned Firm	-------	0.1263 (0.3712)	0.2170 (0.4511)	0.5542 (0.5260)
Post-PDUFA	-------	**0.4049** (0.1862)	**0.5071** (0.2299)	-0.0127 (0.4325)
4-yr Avg of Disease Coverage in *Post*	-------	0.0008 (0.0006)	0.0005 (0.0006)	-0.0013 (0.0012)
Total Groups (Primary Indication)	-------	-------	-0.0023 (0.0032)	-0.0011 (0.0072)
Budget ($M) of Group with Largest Budget	-------	-------	**0.0021** (0.0011)	0.0006 (0.0021)
Groups × Order of Entry	-------	-------	-------	0.0012 (0.0016)
Budget × Order of Tenry	-------	-------	-------	0.0002 (0.0002)
Lethal Disease (Primary Indication)	-------	-------	-------	0.2748 (0.3254)
CDER Staff	-------	-------	-------	**0.0022** (0.0009)
Disease Category Dummy Variables?	No	No	No	Yes
N LLF	447 -263.469	288 -148.547	208 -109.387	207 -99.361

Table 8: Effects of Lobbying, Instrumented by Ownership Features, Pipeline Fraction, and Agreement Propensities

[Maximum likelihood estimates based upon the log-normal duration distribution.]

INSTRUMENTS	β_{lobby} [lobbying variable only]	β_{lobby} [submission variable added]	β_{lobby} [full model]	$\beta_{submits}$ [full model]
Non-Instrumented Lobbying	**-0.0132** (0.0051)	**-**0.0042 (0.0057)	-0.0074 (0.0052)	**-0.0178** (0.0066)
Public Ownership (OLS)	**1.1619** (0.3564)	0.0478 (0.3361)	0.0978 (0.2926)	**0.0233** (0.0064)
Public Ownership (Tobit)	**0.2402** (0.0737)	0.0099 (0.0695)	0.0202 (0.0605)	**0.0233** (0.0064)
Concentration (OLS)	**-0.3601** (0.1809)	-0.0585 (0.1364)	0.0466 (0.1398)	**-0.0228** (0.0062)
Concentration (Tobit)	**-0.0957** (0.0318)	-0.0213 (0.0248)	-0.0067 (0.0253)	**-0.0227** (0.0062)
Pipeline (OLS)	**-0.0787** (0.0377)	**-**0.0327 (0.0257)	-0.0645 (0.0412)	**-0.0218** (0.0066)
Pipeline (Tobit)	**-0.0068** (0.0029)	**-**0.0039 (0.0029)	**-0.0057** (0.0030)	**-0.0217** (0.0068)
Pipeline + Own. + Concent. (OLS)	**-0.0575** (0.0330)	-0.0125 (0.0349)	-0.0424 (0.0334)	**-0.0221** (0.0070)
Pipeline + Own. + Concent. (Tobit)	**-0.0066** (0.0029)	-0.0033 (0.0030)	-0.0056 (0.0035)	**-0.0214** (0.0066)
Agreements net Model 1 (OLS)	0.0015 (0.0166)	0.0096 (0.0165)	-0.0086 (0.0169)	**-0.0243** (0.0070)
Agreements net Model 1 (Tobit)	0.0004 (0.0045)	-0.0026 (0.0045)	-0.0023 (0.0046)	**-0.0242** (0.0070)
Agreements net Model 2 (OLS)	-0.0055 (0.0191)	-0.0006 (0.0189)	-0.0112 (0.0192)	**-0.0242** (0.0070)
Agreements net Model 2 (Tobit)	-0.0014 (0.0049)	-0.0002 (0.0049)	-0.0029 (0.0049)	**-0.0242** (0.0070)

Notes:

- *Pipeline* = % of All Drugs in Development (mid-1990s) that are Preclinical
- *Concentration*: Predicted Values from regression of contributions upon (1) Major Shareholder dummy and (2) Percentage Owned by Major Shareholder
- *Model 1*: Agreements regressed upon sales, merger dummy, firm age, foreign firm dummy, and firm employment
- *Model 2*: Agreements regressed upon sales, merger dummy, foreign firm dummy, and firm employment
- *Full Model* includes mergers, order of entry, orphan drug dummy, CDER staff, foreign firm dummy, firm age, PDUFA dummy, Democratic House majority status, presidential partisanship, and disease category variables.

Note: Number of NDAs = 339-772, depending on instrumentation. Number of firms = 210.

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Figure 1: FDA Review Times for AIDS Drugs, by Order of Entry, 1986-1993

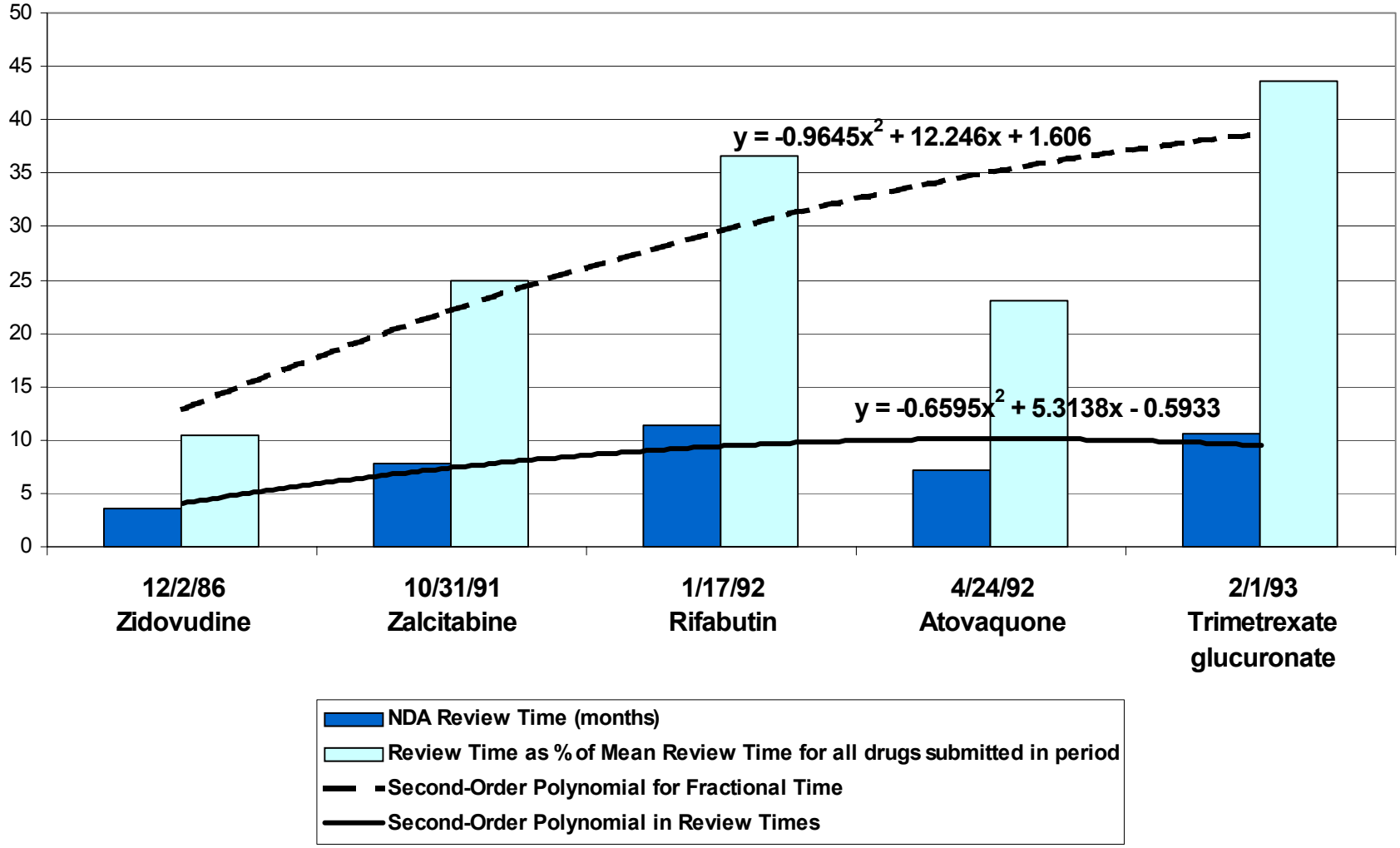


Figure 2: Kaplan-Meier Survivor Function, Stratified by Firm Sales

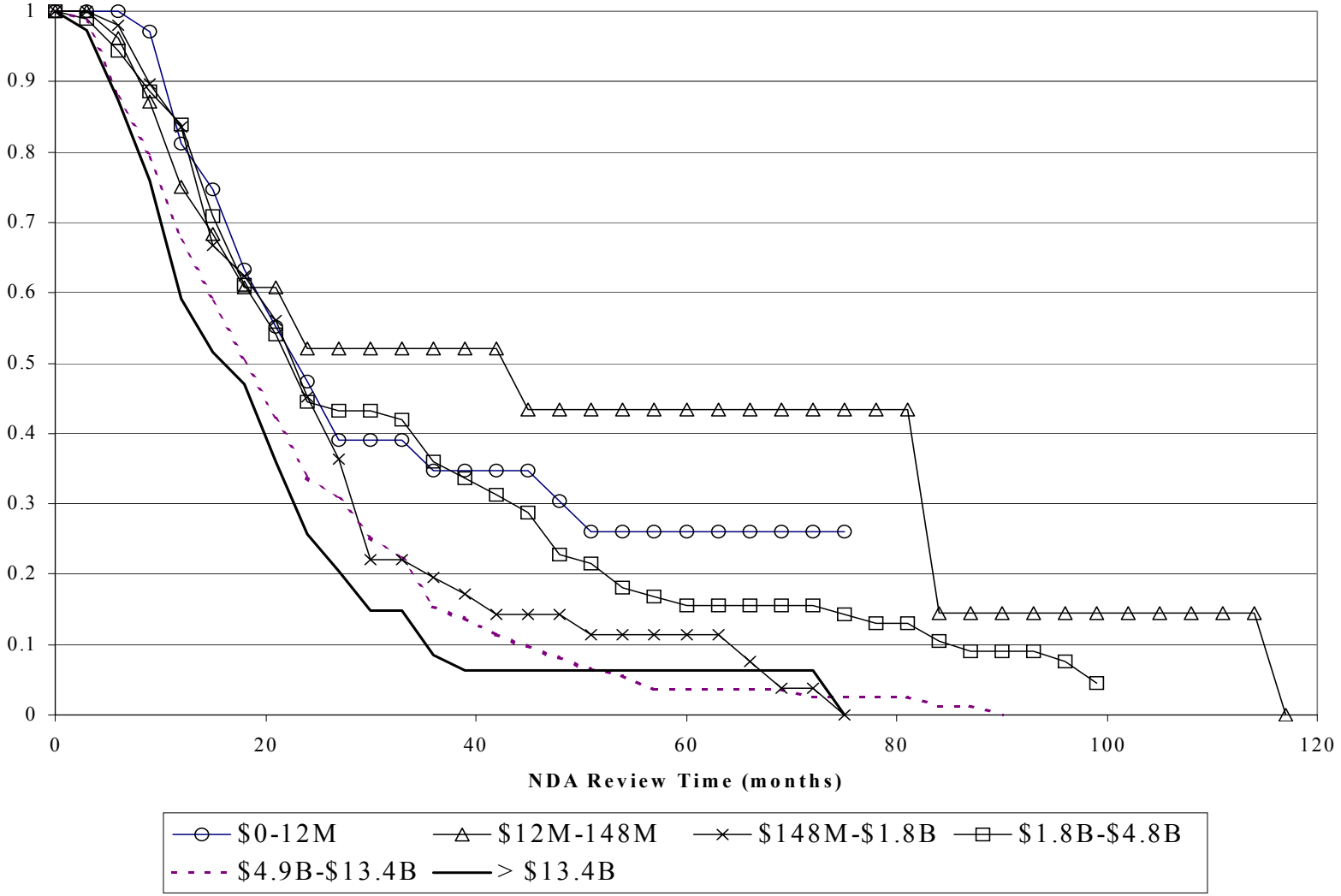


Figure 3: Approval Times by Firm Submissions

[N = 529 NMEs submitted 1979-2000]

