

Approval Times For New Drugs: Does The Source Of Funding For FDA Staff Matter?

The amount of resources devoted to FDA review, not the source of funding, was likely the principal driver behind shrinking approval times since 1980.

by Daniel Carpenter, Michael Chernew, Dean G. Smith, and A. Mark Fendrick

ABSTRACT: The Food and Drug Administration (FDA) has been criticized for injudicious and excessively rapid approval of new drugs as a result of pharmaceutical industry influence. Many critics focus on the Prescription Drug User Fee Act (PDUFA) of 1992, which augmented the FDA's budget through the charging of user fees. We assess the effect of FDA staffing patterns and attributes of submitting firms on approval times for 843 new drug applications (NDAs) submitted between 1977 and 2000. NDA review times shortened by 3.3 months for every 100 additional FDA staff. The amount of funding for FDA staff appears to be a much more important influence on NDA review time than the source of funding.

CRITICS OF THE U.S. FOOD AND DRUG ADMINISTRATION (FDA) contend that recent reductions in drug approval times are attributable to pharmaceutical industry pressure, in part because of the FDA's reliance on industry user fees as mandated by the Prescription Drug User Fee Act (PDUFA) of 1992. Among the more strident critics are Sidney Wolfe of Public Citizen and *Lancet* editor Richard Horton. Horton in particular has questioned the integrity of the FDA, claiming that "the FDA, its Center for Drug Evaluation and Research (CDER) in particular, has become a servant of industry." He remarked that since the passage of PDUFA, "standards for drug approval have declined," and he called for "an independent congressional audit of the FDA's drug approval processes" and a new FDA commissioner who is "demonstrably independent of the pharmaceutical industry."¹

In 2002 the U.S. General Accounting Office (GAO) reported that PDUFA was

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responsible for a decline in review times but also noted that withdrawals of approved drugs had increased both absolutely and proportionally in the wake of PDUFA.² The 2002 GAO report noted that the FDA received approximately \$825 million in user fees from drug and device manufacturers between 1993 and 2001. During that time the mean approval for nonpriority drugs decreased from twenty-seven months to fourteen months. Simultaneously, postapproval recalls increased from 1.56 percent to 5.34 percent. Despite intense debate over the forces accelerating approval times, there is a dearth of published studies that have examined the effect of FDA resources and recent laws upon approval times.³ Accordingly, our aim was to evaluate how the amount and source of FDA funding affected review times before and after the passage of PDUFA, while accounting for FDA staffing patterns, attributes of submitting pharmaceutical firms, and disease-specific attributes of the submitted drugs.

Study Methods

■ **Study sample.** We evaluated new drug applications (NDAs) for 843 new molecular entities (NMEs) submitted to the FDA from 1977 to 2000. NDA review times were gathered from FDA Center for Drug Evaluation and Research (CDER) annual reports, reports of NDA approvals and rejections, and the Pharmaprojects database. Several aspects of our analytic approach are noteworthy. First, unlike many analyses of the FDA review process that include only approved drugs, the study sample also included NMEs that were submitted but not approved ($n = 320$).⁴ Second, the sample excluded generic drugs (Abbreviated New Drug Applications, or ANDAs) and “supplemental” applications (SNDAs) because the NDA review process for NMEs is more comprehensive. Third, approval times were averaged by year of submission (not year of approval), and independent variables were also assigned to NMEs by year of submission. This was done since major parameters of review—the review team, procedures, and NDA priority rating (if any)—are almost always determined at the time of NDA submission.

■ **Study variables.** *FDA resources.* Staffing levels (NDA reviewers and administrators) at the CDER from 1977 to 2000 were measured using the *FDA Directory* for selected years, *A Statistical History of the Food and Drug Administration, FY1938–FY1990*, and the CDER Web site.⁵

Pharmaceutical firm characteristics. To address whether NDA approval times were influenced by specific attributes of pharmaceutical firms, we used two approaches. First, data on sales (from firms’ annual reports and Pharmaprojects), previous NDA submissions, and recent lobbying activity (from the Center for Responsive Politics) were included in the analyses.⁶ In a second set of estimations, we included separate indicator variables (“fixed effects”) for each submitting firm.

Disease burden and characteristics. Several variables were included in the analyses to control for disease burden. Clinical conditions were first classified by body system (for example, cardiovascular, musculoskeletal) and then differentiated into

acute and chronic categories. For each condition, variables were included to account for whether a disease primarily affected men, women, or children. Disease severity was addressed by including the death rate per 1,000 Americans, the number of hospitalizations, and the average length of hospital stay.⁷

■ **Statistical analysis.** The relationship between CDER staffing levels and NME approval time was examined using maximum likelihood duration models.⁸ Our baseline model assumes a Weibull distribution with gamma-distributed frailties (heterogeneity), which have a common component indexed by the primary indication of the NME (the regression analogy here is random effects in a panel model). Other parametric models estimated include lognormal, log-logistic, Gompertz, and gamma distributions, and a Cox (semi-parametric) model was also analyzed. Some analyses included all covariates discussed above, and others included relevant FDA priority ratings of the drug at the time of review (results from several models are described below; a full report of the estimates is available from the authors upon request). Coefficients from the base model were used to estimate drug approval times holding FDA staffing constant at 1980 employment levels ($n = 1,119$), while other variables changed as observed in the data. Because some analyses examine only drugs submitted from 1977 to 1992 (before PDUFA), and because we were not able to retrieve priority ratings for some nonapproved drugs, some estimation samples are smaller than $N = 843$.

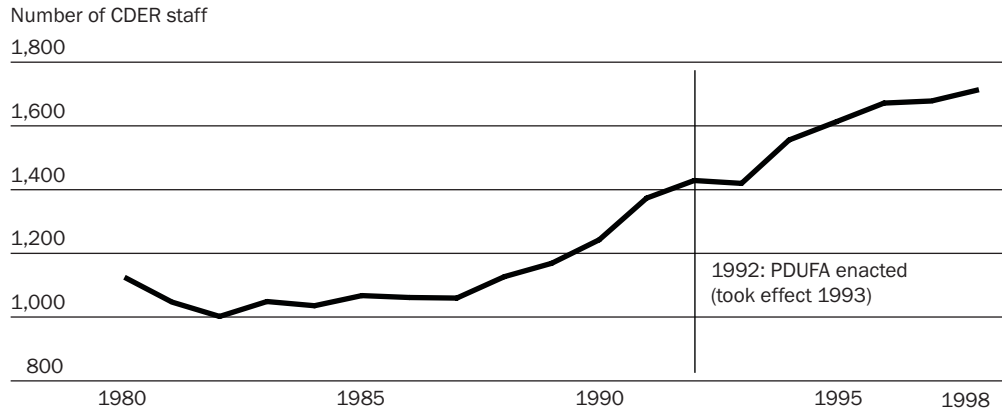
The impact of PDUFA on NDA approval times was evaluated in three related models. To assess how review times were changing prior to PDUFA, a model based on data before enactment of PDUFA (1977–1992) was estimated. A second analysis used the full sample but included a binary variable to test for a post-PDUFA “shift” in approval times. Last, an analysis that examined interactions between the post-PDUFA dummy variable and the firm-specific variables (sales, lobbying, and previous submissions) was undertaken to assess whether the relationship between firm attributes and approval times changed after PDUFA was enacted.

Results

■ **CDER staffing levels.** Exhibit 1 shows CDER staffing between 1977 and 1998. A substantial increase in CDER staff occurred in the five years prior to the passing of PDUFA in 1992.

Over the study period, increases in the number of CDER staff had a significant impact on shortening the duration of NDA reviews. Our different models produced a range of maximum likelihood estimates of marginal effects of CDER staff increases. Our baseline model (fully specified Weibull model) estimated that for every 100 additional CDER employees, the average NDA review time declined by 3.3 months ($z\text{-stat} = -4.2$). The effects estimated from the lognormal model are smaller but still quite substantial at 2.6 months’ reduction in review time ($z\text{-stat} = -3.74$). Many of our statistical analyses yielded much larger marginal-effects estimates. Exhibits 2 and 3 show the hypothetical effect on FDA drug approval times

EXHIBIT 1
Food And Drug Administration (FDA) Center For Drug Evaluation And Research (CDER) Staffing Levels, 1980-1998



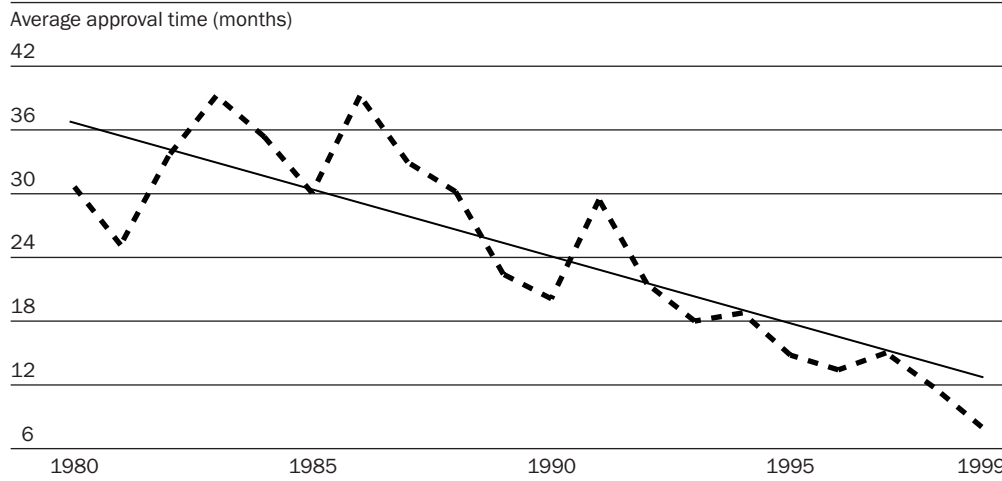
SOURCES: FDA Annual Reports, various years; and P.B. Hutt and S. White, *A Statistical History of the Food and Drug Administration, FY 1938-FY 1990* (Rockville, Md.: U.S. Food and Drug Administration, 1991).

NOTE: PDUFA is the Prescription Drug User Fee Act of 1992.

if no increase in FDA staffing had occurred in the past two decades. Under this scenario, average NDA approval times would today be at twenty-four months, almost a year longer than is actually the case.

We emphasize that this substantial effect of increased staff on shorter approvals began before PDUFA was passed (Exhibit 2). When the NDA sample was restricted to the period prior to the passage of PDUFA (1977-1992), staff size re-

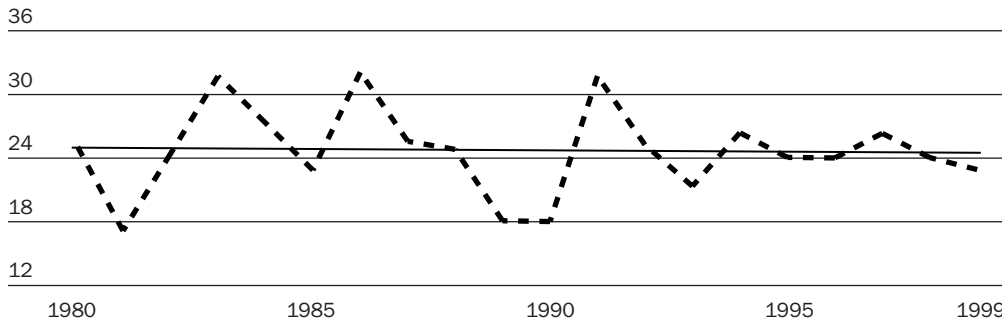
EXHIBIT 2
Actual Decline In New Molecular Entity (NME) Approval Times, Averaged By Year Of Submission To The Food And Drug Administration (FDA), 1980-1999



SOURCES: FDA Annual Reports, various years; and authors' data.

EXHIBIT 3**Average Approval Time For New Molecular Entities (NMEs), By Year Of Submission, With Center For Drug Evaluation And Research (CDER) Staffing Assumed Constant At 1980 Level (N = 1,119), 1980–1999**

Average approval time (months)

**SOURCES:** Food and Drug Administration (FDA) Annual Reports, various years; and authors' data.

mained significant and had an even larger effect size (6.6-month decline for every 100 CDER staff in both Weibull and lognormal models; z -stat = -4.56 in Weibull, -5.17 in lognormal). The model holding CDER staff constant at 1980 levels demonstrates that approval times would have remained largely unchanged in the absence of staff increases before and after PDUFA (Exhibit 3). Models that included the post-PDUFA dummy variable did not infer a statistically significant PDUFA-related “shift” in NDA approval time, which suggests that once staffing is held constant, PDUFA did not result in shorter review times.

■ **Influence of pharmaceutical firm attributes.** We also estimated models that include interactions between firm attributes and either a PDUFA dummy variable or CDER staffing (data not shown).⁹ We find that neither PDUFA nor CDER staffing accelerated drug review for firms with higher sales (z -stat = 0.86 ; $p = .39$), more lobbying activity (z -stat = -1.22 ; $p = .23$), or number of NDA submissions (z -stat = 0.36 ; $p = .72$). In fact, reduced models suggest that approval times may have declined less rapidly for firms with more sales as the FDA's staff resources grew (z -stat = 1.70).

Discussion

Our analyses suggest that the amount of resources devoted to the FDA review process, not the source of funding, was likely the principal driver behind the decline in NDA approval times over the past two decades. This significant effect of enhanced CDER staffing levels on decreasing approval times was substantial and observable several years before PDUFA was passed. Sensitivity analyses performed to explicitly identify effects of PDUFA other than those attributable to increasing staff levels were unrevealing. Moreover, we found no evidence that larger or more politically active pharmaceutical firms fared better in the review process after PDUFA was enacted.

“These findings cast doubt on the argument that the industry’s most powerful firms have benefited disproportionately from PDUFA.”

We acknowledge that the statistical approach used in our analyses was limited in that it did not model and incorporate every aspect of the complex decision-making process at an organization as multifaceted and intricate as the FDA. Our analysis is necessarily observational, not experimental. Although the results cannot entirely rule out some other unobserved causal factor driving reductions in approval times, such as changes in internal workflow processes and decision-making procedures, they remain fully consistent with our hypothesis. Moreover, if the passage of PDUFA, holding staffing levels constant, had a significant impact on approval times, we believe that this effect would have been observed in our analyses, as would a more rapid decrease in approval times after the passage of PDUFA for larger firms. These findings cast doubt on the argument that the pharmaceutical industry’s most powerful firms have benefited disproportionately from PDUFA and that PDUFA-mandated user fees directly promote industry influence.

However, our results do not uphold the industry’s claim that the recent decline in approval times is entirely attributable to user fees.¹⁰ While PDUFA may have further reduced review times, it did so because it increased staff resources at the FDA. We stress that a substantial staff-related decline occurred in the five years before PDUFA’s passage. We strongly believe that nearly all of the decrease in approval times would have been achieved had the FDA been appropriated these funds directly, instead of relying upon industry user fees. Although we cannot determine whether the reduced review times were, on net, beneficial, our results validate the argument that FDA officials voiced before 1992 that additional CDER personnel would be needed to reduce approval times. We conclude that incremental resources provided to the FDA to perform reviews, not the source of the additional funds, drove the important decline in drug approval times over the past two decades.

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NOTES

1. R. Horton, "The FDA and Lotronex: A Fatal Erosion of Integrity," *Lancet* 357, no. 9268 (2001): 1544–1545.
2. See U.S. General Accounting Office, *FDA Review Time for Drugs Has Decreased in Recent Years*, Pub. no. GAO/PEMD-96-1 (Washington: GAO, October 1995); and GAO, *Food and Drug Administration: Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities*, Pub. no. GAO-02-958 (Washington: GAO, 2002).
3. Our analysis is the first to use maximum likelihood multivariate survival analysis. In a forthcoming paper, Mary Olson uses time series analysis to study these effects. M. Olson, "Managing Delegation with User Fees: Reducing Delay in New Drug Review," *Journal of Health Politics, Policy and Law* (forthcoming).
4. Among the many studies that restrict analysis to approved drugs, see K.I. Kaitin, "The Prescription Drug User Fee Act of 1992 and the New Drug Development Process," *American Journal of Therapeutics* 4, no. 5/6 (1977): 167–172; S. Shulman and K.I. Kaitin, "The Prescription Drug User Fee Act of 1992: A Five-Year Experiment for Industry and the FDA," *Pharmacoeconomics* 9, no. 2 (1996): 121–133; J.A. DiMasi and M. Manocchia, "Initiatives to Speed New Drug Development and Regulatory Review: The Impact of FDA-Sponsor Conferences," *Drug Information Journal* 31, no. 3 (1997): 771–788; and D.A. Kessler et al., "Approval of New Drugs in the United States: Comparison with the United Kingdom, Germany, and Japan," *Journal of the American Medical Association* 276, no. 22 (1976): 1826–1831.
5. Food and Drug Law Institute, *FDA Directory* (Washington: Food and Drug Law Institute, selected years 1981–1997); P.B. Hutt and S. White, *A Statistical History of the Food and Drug Administration, FY 1938–FY 1990* (Rockville, Md.: U.S. Food and Drug Administration, 1991); and FDA, Center for Drug Evaluation and Research, www.fda.gov/cder.
6. *Pharmaprojects 2000–2003* (London: PJB Publications, various years). For another study examining the effect of previous NDA submissions upon approval time, see M. Olson, "Firm Characteristics and the Speed of FDA Approval," *Journal of Economics and Management Strategy* (Summer 1997): 377–401.
7. Agency for Healthcare Research and Quality, Healthcare Cost and Utilization Project (HCUP) data, June 2003, hcup.ahrq.gov/HCUPnet.asp (20 November 2003).
8. For a discussion of methodological issues related to such estimations, see D.P. Carpenter, "Groups, the Media, Agency Waiting Costs, and FDA Drug Approval," *American Journal of Political Science* (July 2002): 490–505.
9. Details about these models are available on request; send e-mail to Mark Fendrick, amfen@umich.edu.
10. Pharmaceutical Research and Manufacturers of America, "Patients Are Waiting for Congress to Renew Successful Law That Ensures Prompt F.D.A. Drug Reviews, Says PhRMA," Press Release, 8 March 2002, www.phrma.org/mediaroom/press/releases/08.03.2002.361.cfm (19 November 2003); and testimony of Timothy R. Franson, vice president of clinical research and regulatory affairs—U.S., Eli Lilly Research Laboratories, to U.S. House Committee on Energy and Commerce, Subcommittee on Health, "Reauthorization of the Prescription Drug User Fee Act," 6 March 2002, energycommerce.house.gov/107/hearings/03062002Hearing502/Franson848.htm (19 November 2003).