

INDUSTRY FUNDING OF THE FDA: EFFECTS OF PDUFA ON APPROVAL TIMES AND WITHDRAWAL RATES

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Abstract | The development of new therapies is a crucial component of efforts to improve healthcare. Because drug development and FDA regulatory review have historically been lengthy and costly processes, the US Congress passed a series of legislative acts, beginning in 1992, known collectively as the Prescription Drug User Fee Acts (PDUFA), which sought to expedite the FDA drug-review process. Here, we review data on drug approvals and drug-approval times, both as a whole and by therapeutic class, which demonstrate that implementation of the PDUFAs led to substantial incremental reductions in approval times beyond what would have been observed in the absence of these legislative acts. In addition, our preliminary examination of the trends in the number of new molecular entity withdrawals, frequently used as a proxy to assess the FDA's safety record, suggests that the proportion of approvals ultimately leading to safety withdrawals prior to PDUFA and during PDUFA I and II were not statistically different.

It is well known that drug development is costly, both in terms of time and expense. Recent reports estimate that it takes ~7–9 years to successfully develop a drug at a cost of at least US\$800 million¹. The majority of this development time, 6–7 years, is split up into pre-clinical validation and the clinical phases of development in which safety and efficacy are evaluated. The final requirement in the process of developing a new marketed drug in the United States is the submission to the Food and Drug Administration (FDA) of a New Drug Application (NDA), which is filed for chemical entities, or a Biologics License Application (BLA), which is usually filed for BIOLOGICAL AGENTS (defined as being derived from a living organism)². On the basis of its assessment of a particular NDA/BLA, the FDA issues either an 'approval', 'approvable' or a 'non-approvable' letter to the company/sponsor. Without an 'approval' from the FDA, the drug under review cannot be marketed in the United States. Once tested in humans, the probability of a drug passing both the clinical and regulatory hurdles is estimated to be 20%³.

In addition, only about one-third of the drugs that are developed generate revenues sufficient to recoup the expenses of their development⁴.

The goals of PDUFA. The time for FDA review represents a significant component of the overall time of drug development (see FIG. 1 for trends in drug approval times). In 1992, the US Congress, in an attempt to reduce the time and cost of drug development, enacted the first PDUFA, which authorized the FDA to collect fees from sponsors submitting an NDA or BLA, and enabled the FDA to hire additional review staff to facilitate more rapid review^{5,6}. Congress renewed the 1992 PDUFA legislation under the Food and Drug Modernization Act of 1997 (PDUFA II) and again under the Bioterrorism Preparedness and Response Act of 2002 (PDUFA III)⁷.

According to the PDUFA legislation, in exchange for collection of user fees, the FDA is legally obliged to "review and act on" NDA/BLA submissions, but not necessarily approve them more rapidly. More specifically,

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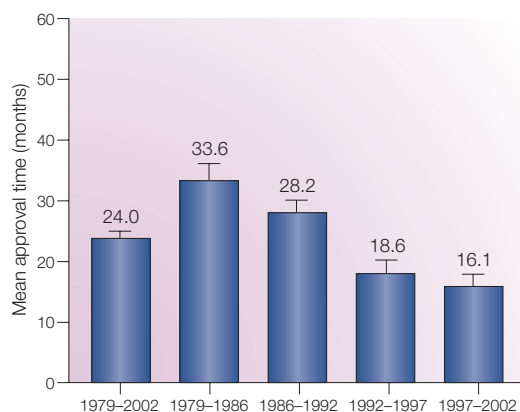


Figure 1 | Mean approval times for NMEs. The average approval time (New Drug Application/Biologic License Application filing to final FDA action of approval) was determined for all NEW MOLECULAR ENTITIES (NMEs) submitted to the FDA from 1 October 1979 to 30 September 2002. Standard deviations were also calculated for each time period. The time periods are defined in line with the government fiscal year to better mirror the enactment of the Prescription Drug User Fee Acts in later time periods.

“review and act on” is understood to mean the issuance of a complete action letter after the complete review of a filed complete application. The action letter, if it is not an approval, will set forth in detail the specific deficiencies and, where appropriate, the actions necessary to place the application in condition for approval⁸.

In essence, PDUFA mandates responses and action letters, not necessarily approvals. Major goals of the various PDUFA legislations are highlighted in TABLE 1. In the case of PDUFA I, II and III, the FDA is obliged to deliver a complete review on 90% of PRIORITY APPLICATIONS within 6 months. Under PDUFA I, the FDA was mandated to review 90% of standard applications in 12 months, and under PDUFA II and III the FDA must review 90% of standard applications in 10 months. In response to submitted NDAs/BLAs, the FDA must issue one of three written actions: a ‘non-approvable’ letter indicating that the application has not satisfied the FDA’s standards for safety and/or efficacy; an ‘approvable’ letter indicating that the filing can be approved if certain deficiencies and questions are answered appropriately; or an ‘approval’ letter granting the sponsor/company the right to market the drug to the public in the United States.

Table 1 | PDUFA I, II and III standard and priority goals for original NDA/BLAs

Goal	PDUFA I	PDUFA II	PDUFA III
Priority review			
Complete review of priority original new drug and biologic applications and efficacy supplements	90% in 6 months	90% in 6 months	90% in 6 months
Standard review			
Complete review of standard original new drug and biologic applications and efficacy supplements	90% in 12 months	90% in 10 months	90% in 10 months

Adapted from REF. 28. Additional goals and specifications for Prescription Drug User Fee Acts (PDUFA) I, II and III can be found on the FDA website. BLA, Biologic License Application; NDA, New Drug Application.

PDUFA fees. PDUFA levies consist of application, establishment and product fees. The application fee is paid to the FDA upon submission of an NDA/BLA. Product fees are paid annually for products that have previously received marketing approval. Establishment fees are assessed annually on approved manufacturing facilities; multiple products can share the burden of one establishment fee.

The application fee with clinical data has had an annual growth rate of 17%, rising from US\$100,000 in 1993 to US\$573,500 in 2004. Similarly, product fees have averaged 17% growth annually, growing from US\$6,000 in 1993 to US\$36,080 in 2004. Establishment fees have averaged 13% growth annually over the past 11 years. The total combined revenue from the PDUFA user fees for the FDA through FISCAL YEAR 2003 is roughly US\$1.2 billion. For the fiscal years 2002 and 2003, the FDA collected roughly US\$142 million and US\$210 million, respectively, in PDUFA fees⁹. The fiscal year 2002 and 2003 programme level budgets for the entire FDA were US\$1.55 billion and US\$1.65 billion respectively. Therefore, PDUFA user fees accounted for approximately 9.2% and 12.7% of the FDA’s entire budget for these years, respectively^{10,11}. Salaries and expenses for the categories of drugs and biologics totalled US\$540 million and US\$624 million in the same 2 years. PDUFA user fees represented 26.3% (2002) and 33.7% (2003) of these budgets. Overall, PDUFA fees make up ~50% of the monies spent on the NDA/BLA review process. Clearly, PDUFA has become a crucial source of funds for the FDA’s operations in supervising the review and approval of new drugs and biologics¹².

User fee programmes also exist at the European Medicines Agency (EMA). Currently the application fee for a single strength and one pharmaceutical form is €232,000, with an additional €23,200 for each additional strength and/or pharmaceutical form. An annual fee of €75,600 is also assessed, and 5-year renewal fees are €11,600¹³. The EMA goal is that ~25% of its funding be derived from the European Commission, and the remaining 75% from user fees¹⁴. By comparison, the UK’s Medicines and Healthcare products Regulatory Agency is entirely funded through user fees, whereas Japan’s regulatory agency, Koseisho, has no user fee programme^{14,15}.

BIOLOGICAL AGENTS

Biologicals include vaccines, monoclonal antibodies and other protein products that are often manufactured using biotechnology methods.

NEW MOLECULAR ENTITY

A medication containing an active substance that has never before been approved for marketing in any form in the United States.

PRIORITY APPLICATION

The FDA designates New Drug Applications as either Standard or Priority. Currently, a Standard designation sets the target date for completing all aspects of a review and the FDA taking an action on the application (approve or not approve) at 10 months after the date it was filed. Currently, a Priority designation sets the target date for the FDA at 6 months. A Priority designation is intended for those products that address unmet medical needs.

FISCAL YEAR

The government fiscal year begins on 1 October and ends on 30 September of the following year.

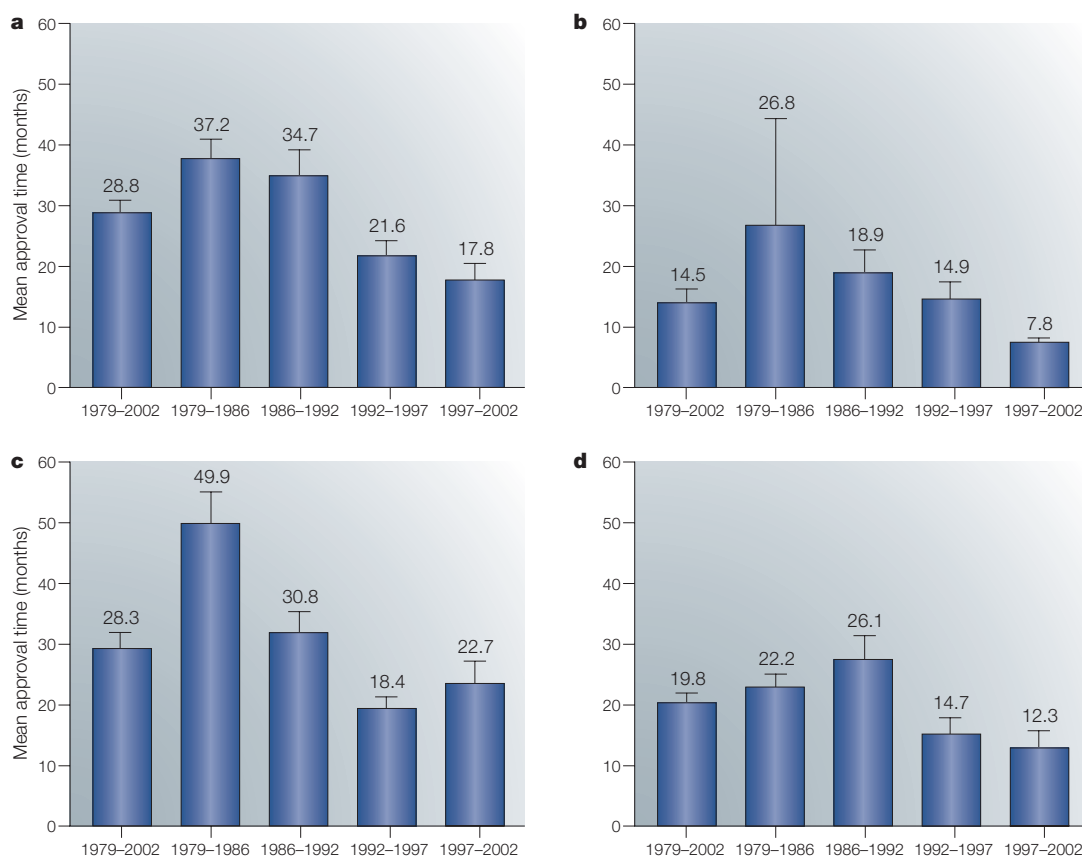


Figure 2 | Mean NME approval times across therapeutic classes. Average approval times were determined for new molecular entities (NMEs) approved between 1 October 1979 to 30 September 2002 and classified as either cardiovascular (a), antineoplastic (b), central nervous system (c) or anti-infective (d). Standard deviations are also calculated for each time period.

Effects of PDUFA. Detractors of PDUFA suggest that payment of user fees by the industry undermines the regulatory abilities of the FDA and has created a federal agency that is beholden to the very companies it is mandated to regulate. Proponents of PDUFA maintain that the FDA's decisions on drug applications are independent of the source of the revenue (see, for example, REF. 5), because user fees from the sponsoring organization are not paid directly to any individual reviewer or division within the agency; rather, monies collected are paid to the FDA as a whole and are distributed via normal budgeting processes.

In an attempt to assess the impact of PDUFAs, in this article we review data on drug approvals and drug approval times over the past 25 years. Although a number of descriptive studies have reported more rapid drug-approval times during the PDUFA era, none has statistically isolated the effects of PDUFA I and II by therapeutic class within a multivariate context as we do here, nor has the impact of PDUFA on drug safety withdrawal rates been assessed. We document that implementation of PDUFA led to substantial incremental reductions in approval times beyond what would have been observed without these acts (6–7% annual declines during PDUFA I and ~3–4% during PDUFA II). A preliminary examination of the trends in the number of new molecular entity (NME)

withdrawals also indicates that the proportion of approvals that ultimately led to safety withdrawals prior to PDUFA and during PDUFA I and II were not statistically different (ranging between 2% and 3%, depending on the method of analysis). Further analysis, including examination of hazard functions and the quantification of number of individuals exposed to new treatments, is needed to better understand the safety implications of PDUFA.

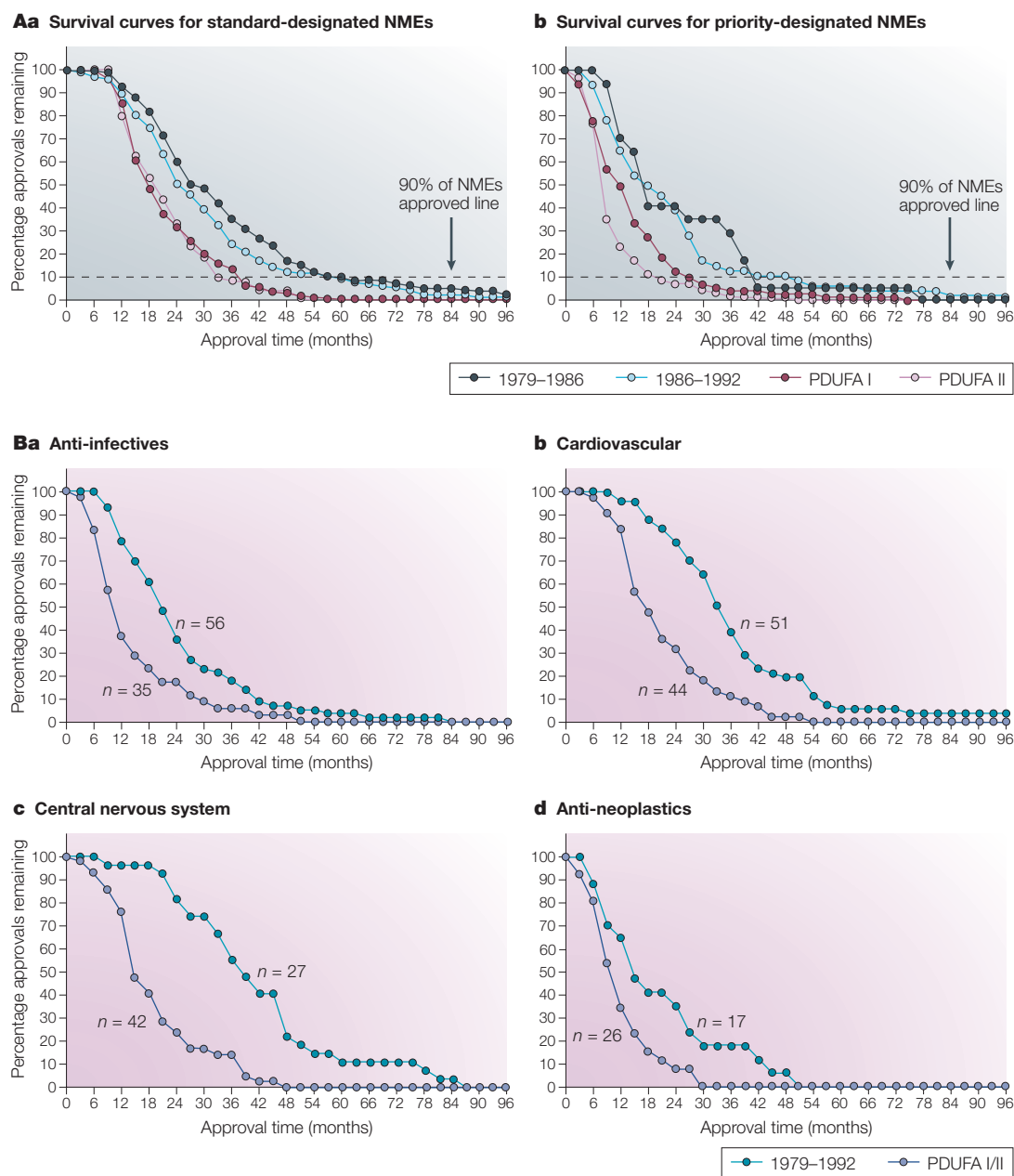
Historical trends in NME approval times

The period from NDA filing to final approval (referred to as the 'approval phase' in this study) is a crucial component in the development of a new therapy, and represents the last hurdle to obtaining marketing authorization. Previously published studies have documented a marked decrease in approval times during the 1990s compared with earlier time periods^{16–21}. Here, we examine approval times covering the entire PDUFA I and II time periods (1992–2002), and compare trends to pre-PDUFA years (1979–1992). Long-term trends in approval times of all submitted and subsequently approved NMEs, which totalled 662 between 1 October 1979 and 30 September 2002, are displayed in FIG. 1. The NMEs are defined here as novel products that include both small molecules (chemically synthesized entities) and biological

agents. The 662 NMEs consist of 534 chemical entities (81%), 90 biological entities (including novel vaccines (14%) and 38 diagnostic entities (6%). Although over the entire time period from 1 October 1979 to 30 September 2002 the mean approval time was 24 months, a downward trend is clearly apparent, with mean approval times decreasing from 33.6 months in the period of 1 October 1979 to 30 September 1986 to 16.1 months during the period from 1 October 1997 to 30 September 2002, a considerable 52% reduction (the government fiscal year was used in the analysis to align with the PDUFA funding time periods).

Trends in NME approvals

To document the pervasiveness of this reduction in NDA/BLA approval times across therapeutic classes, NME approval times were calculated separately for cardiovascular, antineoplastic, central nervous system (CNS) and anti-infective drugs (FIG. 2). These four therapeutic classes represent 298 (45%) of the 662 NMEs submitted and subsequently approved between 1 October 1979 and 30 September 2002. Mean cardiovascular NME approval times declined steadily from 37.2 months in 1979–1986 to 17.8 months in 1997–2002, representing a 52% decrease



SURVIVAL CURVE
A curve measuring the percentage of subjects in a cohort that survive from one time period to the next, technically known as Kaplan–Meier survival functions. Survival functions take into account censoring — data points that are unobservable.

Figure 3 | ‘Survival’ curves for NMEs. **Aa** | SURVIVAL CURVE for ‘standard’ NMEs. **Ab** | Survival curve for ‘priority’ NMEs. **B** | Therapeutic class ‘survival’ curves: anti-infectives (**a**), cardiovascular (**b**), central nervous system (**c**) and antineoplastics (**d**). NME, new molecular entity; PDUFA, Prescription Drug User Fee Act.

Table 2 | Impact of PDUFAs on approval times: regression variables and results

Variable	Aggregate specification for PDUFA time trends		Drug-class specification for PDUFA time trends	
	Coefficient	p value	Coefficient	p value
Intercept constant	3.515	<0.001	3.524	<0.001
Natural Log IND to NDA time	-0.001	0.965	-0.012	0.695
Time trend	-0.017	0.038	-0.016	0.050
Priority Review	-0.490	<0.001	-0.487	<0.001
PDUFA I time trend	-0.081	0.001	-0.080	0.001
PDUFA II time trend	-0.037	0.018	-0.029	0.062
IND to NDA data missing	0.103	0.521	0.055	0.728
Orphan Drug	0.109	0.094	0.114	0.078
Domestic company sponsor	-0.072	0.115	-0.074	0.100
Cardiovascular	0.120	0.203	0.136	0.144
Anti-infectives	-0.306	0.001	-0.294	0.002
Antineoplastics	-0.304	0.009	-0.143	0.276
Central nervous system	0.128	0.211	0.143	0.159
AIDS	-0.812	<0.001	-0.805	<0.001
Metabolic/endocrine	-0.062	0.514	-0.056	0.550
Gastrointestinal	-0.088	0.516	-0.069	0.607
Dermatology/ophtalmology	-0.188	0.087	-0.179	0.101
Anti-inflammatories	0.101	0.505	0.322	0.061
Radiopharmaceuticals	0.183	0.122	0.202	0.085
Respiratory	0.288	0.041	0.309	0.027
Other	-0.352	0.019	-0.334	0.025
Anti-inflammatory PDUFA II time trend	N/A	N/A	-0.114	0.007
Antineoplastic PDUFA II time trend	N/A	N/A	-0.064	0.011
R-squared	0.393		0.405	
Observations	662		662	

IND, Investigational New Drug application; NDA, New Drug Application; PDUFA, Prescription Drug User Fee Act.

(FIG. 2a). Approval times for antineoplastic agents decreased by 71%, from 26.8 months in 1979–1986 to 7.8 months in 1997–2002 (FIG. 2b). Mean NME approval times for treating CNS conditions decreased from 49.9 months in 1979–1986 to 22.7 months in 1997–2002, representing a 54% decrease (FIG. 2c), although mean approval times during PDUFA II were greater than in PDUFA I (22.7 versus 16.4 months). Finally, mean approval times for anti-infective agents decreased from 22.2 months in 1979–1986 to 12.3 months in 1997–2002 (FIG. 2d). This 44% reduction is the lowest proportional decrease among the classes analysed here. The relatively small decrease for anti-infectives probably reflects the pre-existing short approval times for this class. Together, these findings suggest that over the past quarter of a century, approval times decreased both prior to and during PDUFA. However, they do not enable one to reach conclusions about the incremental effects of PDUFA on approval times.

FDA performance goals

As noted earlier, Congress mandated that the FDA meet performance goals consisting of response and action letters, not necessarily approvals. One way of assessing whether the indirect action timeline goals actually translated into reduced approval times is to plot approval time duration in months against the proportion of remaining approvals, or, alternatively, against the attrition rate of remaining approvals, which is roughly analogous to a survival curve; although not a true survival curve (typically based on estimated hazard functions), these curves illuminate the impact of PDUFA on drug approval timelines.

FIGURE 3Aa shows the survival curves for standard-designated NME applications submitted during 1 October 1979 to 30 September 1986, 1 October 1986 to 30 August 1992 (PDUFA I was legislated to take effect on 1 September 1992, not 1 October 1992), 1 September 1992 to 30 September 1997 (PDUFA I) and 1 October 1997 to 30 September 2002 (PDUFA II).

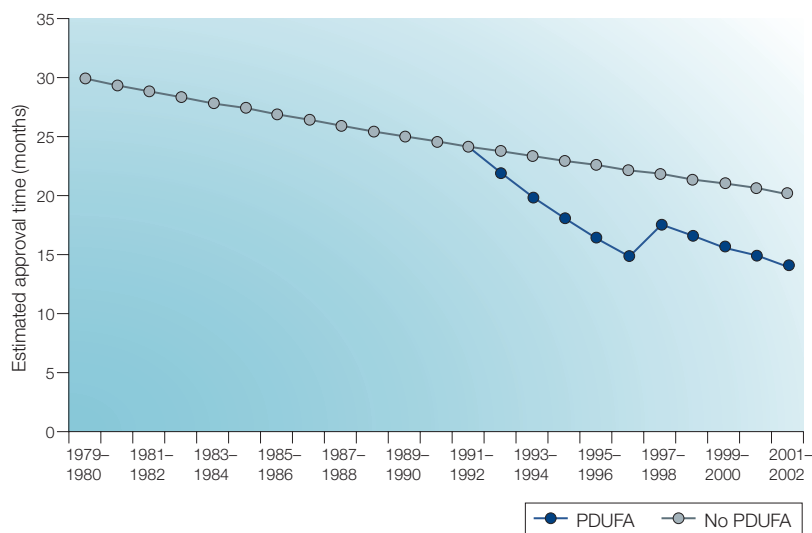


Figure 4 | Impact of PDUFAs on drug approval times. The graph shows estimated NME approval times with and without PDUFAs, based on multivariate linear regression. NME, new molecular entity; PDUFA, Prescription Drug User Fee Act.

These curves are ever closer to the origin, implying that after the passage of any given amount of time, the proportion of remaining approvals steadily declined; whereas 10% remaining (90% approved) occurred after about 60 months prior to PDUFA, during PDUFA I, this time interval fell to about 37 months, and decreased further during PDUFA II to 32 months. FIG. 3Ab shows even larger proportionate reductions for priority-designated NME applications. Note that the 90th percentiles of these survival-time distributions do not coincide with the PDUFA goals because those goals were not focused on approval times, but rather on action-response times.

This decrease in approval times is also evident when the same survival curve graphical analysis is applied to the anti-infective, cardiovascular, CNS and antineoplastic therapeutic classes (FIG. 3B; consolidated standard and priority NMEs). CNS and cardiovascular therapeutic areas have the greatest separation between pre-PDUFA and PDUFA periods. However, the anti-neoplastic and anti-infective therapies are approved more rapidly than the CNS and cardiovascular drugs. This is probably because of the chronic treatment of many of the CNS and cardiovascular indications, as well as urgent unmet needs in oncology.

Impact of PDUFA on NME approval times

As noted earlier, other researchers have documented that NME approval times have decreased during the time period coinciding with the PDUFA legislation (see REFS 16–19 for example). However, we are not aware of any quantitative empirical assessment of the incremental impact PDUFA has had on this decrease in approval times, by therapeutic class.

To investigate this, we undertook a multivariate linear regression analysis of the 662 NMEs — small-molecule chemicals and biological agents — submitted to the FDA for review between 1 October 1979 and 30

September 2002 (we used the period of 1 October of one year to 30 September of a following year to mirror the government's fiscal year, except for fiscal year 1993 for the reason noted above). The natural logarithm of the time between NDA/BLA submission and final FDA approval was the dependent variable (for further details on the methods and results of the econometric regression model, see REF. 22). An annual time trend counter variable (1979 = 1, 2002 = 23) is included as a regressor, as are 0–1 PDUFA I and II binary variables (variables with a value 0 or 1); the latter two interacted with another time trend counter (1992/1993 = 1, 2001/2002 = 10) (when the square of the time trend counter was added as a regressor, the coefficient estimate was statistically insignificant (p value of 0.49); this variable is therefore omitted in the preferred specifications). Because factors other than PDUFA are likely to have affected NME approval times (for example, efforts by oncology and HIV/AIDS patient advocacy groups), a number of potentially confounding variables were added as explanatory variables; these additional variables included 0–1 binary variables for whether the application was submitted under the ORPHAN DRUG ACT provisions, whether the application was designated priority review status, and whether the sponsor was domestic or foreign. To account for clinical difficulties in the development process, the time in clinical development (natural logarithm of time between the initial Investigational New Drug application (IND) and the NDA/BLA submission) was added as a regressor (an IND had not been filed, or IND data were simply missing, in 41 of the 662 NME submissions and a 0–1 binary variable was added to flag these observations), as were 0–1 binary variables for 12 therapeutic classes (cardiovascular, anti-infective, antineoplastic, CNS, AIDS, metabolic/endocrine, gastrointestinal, dermatology/ophthalmology, anti-inflammatory, radiopharmaceuticals, respiratory and other, with biologics being the omitted reference case). To allow for therapeutic-class-specific time trends, each of the 12 therapeutic class binary variables was multiplied by the PDUFA I and II time trend interaction variables, thereby creating PDUFA I/II-time interaction variables.

Preliminary regression analysis revealed that in only two therapeutic areas — anti-inflammatory and antineoplastic — were PDUFA-related time trends different from the overall trends. Regression results with and without the differential anti-inflammatory and antineoplastic PDUFA-related trends are given in TABLE 2.

In the specification assuming equal time trends across therapeutic classes (the first column of TABLE 2), the parameter estimate on the overall time trend suggests an annual decline of about 1.7% in approval times; the negative coefficients on the PDUFA I and II variables imply that this decline accelerated to ~9–10% annually during PDUFA I, and then declined at a slightly slower rate of ~5% during PDUFA II (the PDUFA I calculation here involves adding -0.081 to $-0.017 = -0.098$, and exponentiating that, and subtracting 1.0, which yields a decline of -0.093 . Similar calculations were done for PDUFA II). When differential therapeutic class

ORPHAN DRUG ACT
Signed into law in the US on January 4, 1983, the intent of the Orphan Drug Act is to stimulate the research, development and approval of products that treat rare diseases affecting fewer than 200,000 Americans.

Table 3 | NME safety withdrawals according to CDER

Drug name	Submission date	Year approved	Year withdrawn
Fenfluramine	03 Mar 1967	1973	1997
Azaribine	17 Dec 1969	1975	1976
Ticrynafen	15 Nov 1977	1979	1980
Zomepirac	10 Nov 1978	1980	1983
Benoxaprofen	23 Jan 1980	1982	1982
Nomifensine	16 Mar 1979	1984	1986
Suprofen	10 Nov 1978	1985	1987
Terfenadine	01 Mar 1983	1985	1998
Encainide	13 Jan 1984	1986	1991
Astemizole	25 Feb 1985	1988	1999
Flosequinan	01 Oct 1990	1992	1993
Temafloxacin	30 Nov 1989	1992	1992
Cisapride	29 Aug 1991	1993	2000
Dexfenfluramine*	Unavailable	1996	1997
Bromfenac	30 Dec 1994	1997	1998
Cerivastatin	26 Jul 1996	1997	2001
Grepafloxin	08 Nov 1996	1997	1999
Mibefradil	11 Mar 1996	1997	1998
Troglitazone	01 Aug 1996	1997	2000
Rapacuronium	25 Jun 1998	1999	2001
Rofecoxib [†]	23 Nov 1998	1999	2004
Alosetron [§]	30 Jun 1999	2000	2000

*Not considered a new molecular entity (NME). [†]Not in the Center for Drug Research and Evaluation's report. [§]Returned to the market in 2002 with restrictions. Nine NMEs were withdrawn between 1980 and 1992 and include zomepirac, benoxaprofen, nomifensine, suprofen, terfenadine, encainide, astemizole, flosequinan and temafloxacin. For the period 1993–2004, CDER reported on nine withdrawals in their report — ten when Vioxx (rofecoxib) is included. However, one of the withdrawals is not considered an NME and a second drug, alosetron, that was withdrawn from market was reintroduced with distribution restrictions. Data adapted from REF. 25.

PDUFA-related time trends are permitted, for the anti-inflammatory and antineoplastic classes (the second set of columns in TABLE 2), the pre-PDUFA and post-PDUFA annual declines for most therapeutic classes remain about the same as in the more restricted specification; the corresponding coefficient estimates do not change substantially. However, during PDUFA II, the annual declines in approval time for anti-inflammatory drugs approach 15%, whereas those for antineoplastic agents reach about 10% (this estimate is obtained by summing the coefficient estimates on the time trend, PDUFA II time trend, and anti-inflammatory PDUFA II time trend or antineoplastic PDUFA II time trend variables, and then exponentiating, as noted above). In both specifications, as expected, the regression analysis revealed shorter approval times for priority versus standard review (-0.490 exponentiated, $\sim 38\%$).

In terms of therapeutic class effects, recall that the regression coefficients are relative to the biologics class. Controlling for other confounding variables, approval times were shortest for AIDS applications (about 56% shorter than biologics), about 30% shorter for the 'other' class, and about 25% shorter for applications in

the anti-infective and antineoplastic therapeutic classes; each of these was statistically significantly shorter than approval times for biologics (p values < 0.05). The only class for which approval times were significantly longer than biologics both pre- and post-PDUFA was respiratory agents ($\sim 33\%$ longer).

One way in which the impact of PDUFA on drug approval times can be envisaged is by plotting predicted approval times from the estimated regression equation (the first set of columns in TABLE 2), with and without the PDUFA-time trend variables set to zero, where all other explanatory variables are evaluated at their sample means. As seen in FIG. 4, in the absence of PDUFA, approval times would have declined at about 1.7% annually, from about 30 months in 1979 to about 20 months in 2002. With PDUFA I and II, however, predicted approval times fell more rapidly, from about 25 months in 1992 to slightly less than 15 months in 2002, representing an approximate 25% reduction from the 20-month average approval time that would have occurred in 2002 without PDUFA.

Withdrawal rates of drugs

Given the recent safety concerns over the cyclooxygenase 2 (COX2) inhibitors rofecoxib (Vioxx; Merck) and celecoxib (Celebrex; Pfizer), controversies concerning the issue of whether the FDA has been approving drugs too quickly and without adequate review have re-emerged (for an FDA analysis of safety withdrawals up to 1998, see REF. 23). A 2002 study conducted by the Government Accountability Office (GAO), formerly the General Accounting Office, analysed withdrawal rates prior to and during PDUFA up to 2002. The GAO found that 6 out of 193 (3.10%) NMEs approved from 1986 to 1992 (calendar year periods) were withdrawn for safety-related reasons. During the period 1993–2000 (calendar year periods), 9 out of 259 (3.47%) NMEs approved by the FDA were ultimately withdrawn²⁴. A comparison of proportions test using a simple medical statistics calculator (see Further information online) to compare the proportions gives a p value = 0.9615, which means that the null hypothesis that the proportions are equal cannot be rejected. The GAO study focused only on chemical NMEs (NCEs), and did not take into account approvals of biologics.

If biologics are included in the NME approval counts, then 320 NMEs were approved between calendar years 1980–1992 (the list of biologics was provided by E. Hass at the FDA and is derived from PhRMA's annual NME report published in January of every year). Of these approvals, nine (zomepirac, benoxaprofen, nomifensine, suprofen, terfenadine, encainide, astemizole, flosequinan and temafloxacin) were eventually withdrawn for safety reasons. For the period of calendar years 1993–2002, 361 NMEs were approved, out of which eight (cisapride, bromfenac, cerivastatin, grepafloxin, mibefradil, troglitazone, rapacuronium and rofecoxib) were withdrawn for safety reasons. Note that dexfenfluramine and alosetron, although included on the Center for Drug Evaluation and Research's (CDER's) list (TABLE 3), are not included in this analysis because dexfenfluramine was

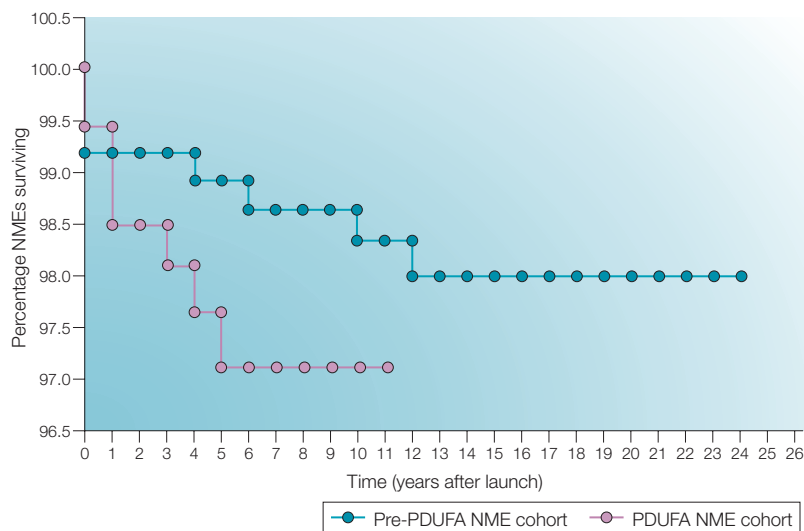


Figure 5 | **Kaplan–Meier survival curve analysis of drug withdrawals.** The Kaplan–Meier analysis was performed using STATA. NME, new molecular entity; PDUFA, Prescription Drug User Fee Act.

not considered to be an NME and alosetron was eventually returned to the market. Comparison of the 9 out of 320 (2.81%) withdrawn in 1980–1992 to the 8 out of 361 (2.21%) withdrawn in 1993–2002 indicates that the proportions are not statistically different (comparison of proportions test p value = 0.8011, which means that the null hypothesis that proportions are equal cannot be rejected). If the rotavirus vaccine, a biologic not included in CDER’s report that was approved on 31 August 1998 and withdrawn on 15 September 1999, is included in the post-PDUFA analysis, 9 out of 361 (2.49%) NMEs were

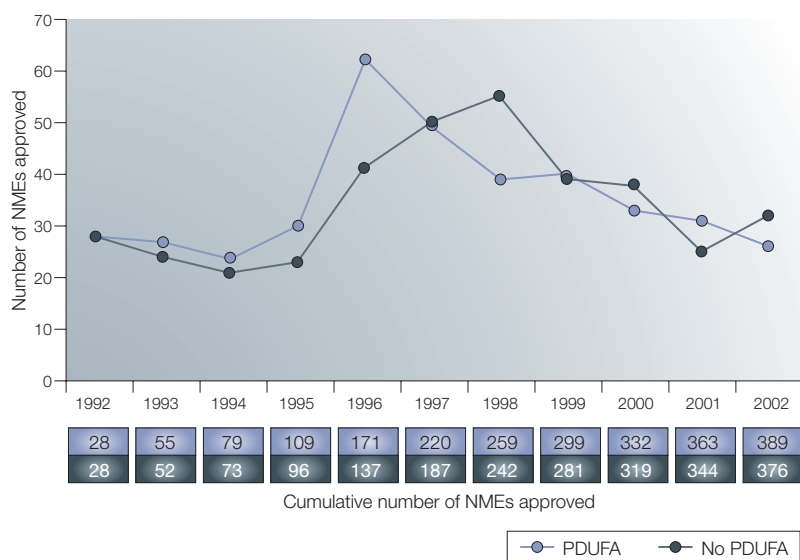


Figure 6 | **Impact of PDUFAs on the annual number of drug approvals.** The graphs compare the number of NME approvals with or without (estimated) PDUFAs by calendar year. The cumulative number of NMEs approved since 1992 with or without (estimated) PDUFAs is shown below. NME, new molecular entity; PDUFA, Prescription Drug User Fee Act.

withdrawn from market (p value = 0.9836 for comparison to pre-PDUFA; cannot reject null hypothesis that proportions are equal).

In its own analysis, the FDA reports slightly different accruals but with qualitatively similar results. The FDA reports that 13 out of 477 NMEs (2.7%) approved between 1 January 1971 and 31 December 1993 were eventually withdrawn for safety reasons, compared with 7 out of 303 NMEs (2.3%) between 1 January 1994 and 30 April 2004²⁵. The FDA believes that virtually all drugs approved during this later time period were reviewed under PDUFA guidelines. Over the 13-year period 1980–1992 (calendar years), roughly 25 drugs were approved per year compared with 31 per year over the 11-year period 1993–2003 (calendar years).

Although the proportion comparisons provide some simple insights, a Kaplan–Meier survival analysis on drug applications submitted to the FDA between 1 January 1980 and 31 August 1992 (termed pre-PDUFA; $n = 365$) compared with drug applications submitted to the FDA between 1 September 1992 and 31 December 2003 (termed post-PDUFA; $n = 351$) indicates that pre-PDUFA drugs have a 98% survival rate (2% withdrawn) compared with a 97.1% survival rate (2.9% withdrawn) for post-PDUFA drugs (FIG. 5), and that based on the log-rank test, these survival curves are not significantly different (p value of no difference = 0.39). The seven drugs withdrawn in the pre-PDUFA period were benoxaprofen, terfenadine, encainide, astemizole, temafloxacin, flosequinan and cisapride. The eight drugs withdrawn in the post-PDUFA period were bromfenac, mibefradil, cerivastatin, troglitazone, grepafloxacin, rotavirus vaccine (we include this in this particular analysis as well given that we accrue biologics as part of the NME count), rapacuronium and rofecoxib.

The various comparisons highlight analytical issues of what to include in the numerator and denominator of the proportion calculations when comparing safety withdrawals prior to and during PDUFA, and how to account for differential exposure time on the market. Specifically, it is not clear when the FDA was able to implement PDUFA, and there is therefore a grey area between the passage of the legislation in 1992 and the actual effects that probably began some time in 1993. This temporal ambiguity can switch several drugs (for example, temafloxacin and cisapride) into either pre- or post-PDUFA, depending on how one interprets the data. Additionally, it is not clear how far the analysis should go back prior to PDUFA. This can significantly alter both the counts of NMEs and withdrawals. Finally, the CDER list of safety withdrawals does not account for products that have troublesome safety profiles with negligible sales that are quietly removed from the market years later without public attention. Given that safety withdrawals are relatively rare events, it is inherently difficult to detect significant differences in withdrawal rates pre- and post-PDUFA.

On the basis of this preliminary analysis, and with these ambiguities as caveats, it seems that withdrawal rates have not changed significantly during the pre- and post-PDUFA time periods. If one takes the

NME drug-withdrawal rate as a proxy for the thoroughness of the FDA's safety assessment during the drug approval and review process, the evidence presented here suggests that the more rapid review of NMEs by the FDA post-PDUFA does not seem to have had any detrimental incremental impact on safety. Interestingly, although FIG. 5 suggests that survival rates of pre- and post-PDUFA approvals are eventually similar, it also suggests that safety withdrawals in the post-PDUFA era have taken place more rapidly, at least in terms of calendar time. This more rapid withdrawal phenomenon could reflect the plausible trend that sales of new therapies have accelerated forward in time during the post-PDUFA era. Whether the number of patients exposed to new therapies prior to safety withdrawal has increased or decreased since PDUFA is an issue that merits further analysis.

Although our analysis is preliminary and invites further and more detailed examinations, in particular using hazard functions, we note that safety withdrawals are relatively rare, and, given that there seems to be some inherent ambiguity in how one measures both the numerator and the denominator of the withdrawal rate pre- and post-PDUFA, it will be challenging to reach unambiguous and statistically significant findings concerning the impact of PDUFA on safety withdrawal rates.

A world without PDUFA

What if PDUFA had never been enacted? How different would the time trend of NME approvals have been and, in particular, would the post-1996 slowdown in NME approvals have been mitigated or exacerbated? These issues can be illuminated by using the multivariate regression model, and predicting for each NME in the sample what the approval date and therefore approval time duration would have been in the absence of PDUFA, assuming that the original date of submission of the NME was unaffected by implementation of PDUFA in 1992. Results of such an analysis, based on the equal proportional PDUFA impact across therapeutic class specification in TABLE 2, are displayed in FIG. 6 according to calendar year. Without PDUFA, the spike in NME approvals that occurred in calendar year 1996 (a total of 62) would have been delayed to calendar year 1998, and because of the idiosyncratic time pattern of NME submissions, the spike would have been slightly smaller — a total of 55 NMEs. Instead of there having been 62 NME approvals in calendar year 1996, there would only have been 41 had PDUFA not been implemented. Moreover, from calendar year 1999 onwards, the number of NME approvals would have fallen to levels very similar to those actually observed. Note also that in the absence of PDUFA, the 'productivity growth slowdown' of R&D would have been less severe — from a high of 55 in 1998 to 32 in 2002, rather than from 62 in 1996 to 26 in 2002.

Another way in which the effects of PDUFA on accelerating NME approval times can be assessed is to calculate, by calendar year since 1992, the cumulative number of new NMEs approved. As seen at the bottom

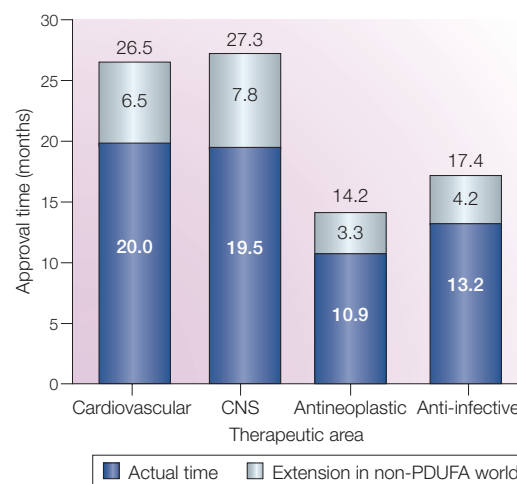


Figure 7 | **Average NME approval times by therapeutic class with predicted average delays.** CNS, central nervous system; NME, new molecular entity; PDUFA, Prescription Drug User Fee Act.

of FIG. 6, at the expiry of PDUFA I in 1997, had that legislation not been enacted and implemented the cumulative number of NMEs approved since 1992 would have been 187, rather than the actual 220 — a reduction of 33 NMEs (or 15%). By the end of 2002, when PDUFA II expired, the cumulative number of NMEs approved since 1992 in the absence of PDUFA I and II would have been 376, 13 (or 3.3%) less than the 389 that actually occurred. So, in a world without PDUFA, many patient lives would have been negatively affected by the delay in gaining access to new therapies.

Finally, to examine variations across therapeutic classes, we use the regression model and similar methodology in the first set of columns in TABLE 2 to predict the extension/delay in approval times in the absence of PDUFA I/II for four therapeutic classes (FIG. 7). As seen in the figure, although actual mean approval times for cardiovascular and CNS NMEs were 20.0 and 19.5 months, without PDUFA these approval times would have been 26.5 and 27.3 months — more than 30% longer. Without PDUFA, the mean approval times for the antineoplastic and anti-infective NMEs would have been 14.2 and 17.3 months, respectively, instead of the actual 10.9 and 13.2 months — an increase of about 30%.

A roadmap to the future

The time required for an NDA to be approved by the FDA is at its lowest level in approximately 30 years. The benefit of a shorter approval translates into more rapid access to drugs by the patients that need them. Although further analyses are clearly warranted, our preliminary analyses indicate that PDUFA I and II have had a significant impact on reducing approval times since 1993, apparently (but not definitively) without having a significant incremental impact on NME safety withdrawal rates. Elsewhere, we examine measurement issues in quantifying the size of the full economic benefits and costs of PDUFA²⁶.

The success of PDUFA in reducing approval times provides a precedent to establish other procedures and processes to reduce the time it takes to develop a new drug therapy. Passage of the Medical Device User Fee and Modernization Act (MDUFMA) of 2002 instituted user fees for pre-market reviews of medical devices, and the Animal Drug User Fee Act of 2003 (ADUFA) provides similar user fees for animal drug applications. A recent survey of both the FDA and senior industry R&D personnel reveals considerable interest in establishing a user fee programme that would facilitate more frequent communication during the clinical phases of drug development, not just the application review portion²⁷. Although such a system would need to be

carefully designed to avoid perverse incentives, it might prove useful in not only shortening development time but also in increasing the probability of final approval, thereby augmenting the supply of new therapies.

Although we remain optimistic that the FDA and industry can cooperate to ensure that new medicines make it to patients safely and expeditiously, we also believe that more funds and efforts need to be devoted to monitoring the safety of drugs post-approval. As part of this study we attempted to assess the number of Phase IV studies devoted to safety, but we have been unable to form an accurate and reliable set of measures of these safety-related efforts. We urge that this issue receive close attention in future research.

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References 20 and 21 discuss results from multivariate statistical analyses of drug-approval times.

An FDA analysis of drug safety withdrawals up to 1998.

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Competing interests statement

The authors declare **competing financial interests**: see Web version for details.

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