

MEASURING THE PACE OF NEW DRUG DEVELOPMENT IN THE USER FEE ERA

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The Prescription Drug User Fee Act of 1992 (PDUFA) is credited with the dramatic reduction in new drug approval times seen since 1993. Despite the faster approval times, however, the total time required for new drugs to reach the marketplace had not changed appreciably. With passage of the FDA Modernization Act of 1997 (FDAMA), the United States Food and Drug Administration (FDA) expanded its focus from shortening the regulatory review phase to helping drug developers reduce lengthy clinical development times and increase the speed to market for new products. Our analyses document a sharp downward trend in approval times during the 1990s—average approval time for new drugs fell 58%, from 31.3 months in the period 1990 to 1991 to 13.2 months in the period 1998 to 1999. Moreover, the percentage of new drugs approved in less than six months increased from 4% in 1992 to 28% in 1999. The data also show that, while average clinical development times increased by 14% from the period 1990 to 1991 to the period 1994 to 1995, there was a 37% decrease from the 1994 to 1995 period to the 1998 to 1999 period. The direction of change in average clinical development time from the first half of the 1990s to the second half varied by therapeutic class and by clinical development phase.

Key Words: New chemical entity; Drug development; New drug approval; Pharmaceutical industry; Food and Drug Administration; Prescription Drug User Fee Act of 1992; FDA Modernization Act of 1997

INTRODUCTION

THERE ARE UNPRECEDENTED challenges and opportunities for the research-based pharmaceutical industry. Economic, scientific, and regulatory factors have fundamentally changed the environment in which innovative pharmaceutical firms operate. For example, worldwide concern over rising

health care expenditures, the rapid growth in managed care organizations, the spiraling increase in generic competition, and the proliferation of cost containment policies—such as restrictive formularies, therapeutic substitution, and mandatory rebates—have substantially increased competitive pressures on drug developers. Today, drug firms must demonstrate that their products are not only safe and effective, but that they offer therapeutic or cost advantages over available therapies.

Scientific factors, such as the changing focus of drug discovery and development and

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the use of new technologies for identifying and screening candidates for drug development, have created new challenges for the research-based drug industry, as well. Whereas in earlier decades, drug firms concentrated primarily on the development of treatments for infection and other acute indications, now they are using state-of-the-art technologies, such as combinatorial chemistry, high-throughput screening, and pharmacogenomics, for targeting diseases of greater complexity and chronicity. The drug development process for many of these persistent, degenerative, and life-threatening diseases is typically longer, more expensive, and more complicated.

The regulatory environment has also influenced pharmaceutical innovation. Regulatory reform and harmonization efforts in the United States, Europe, and Japan reflect a new spirit of industry-agency partnership and an emphasis on improving regulatory efficiency globally. For example, the International Conference on Harmonization (ICH) has provided more than 40 final guidelines in the safety, efficacy, and quality areas that standardize technical requirements for new drug approval in the three major pharmaceutical markets: Europe, the United States, and Japan. Moreover, at its July 1997 meeting in Brussels, ICH initiated efforts to create a Common Technical Document. When completed, this effort will allow firms to produce a technical information package, with standardized format and content, that can be submitted in all three ICH regions.

In the United States, regulatory initiatives have provided valuable opportunities for pharmaceutical developers as they work to improve efficiency. For example, in the years following implementation of the Prescription Drug User Fee Act of 1992 (1), which authorized the collection of user fees by the Food and Drug Administration to review marketing applications for new drugs, there has been a sharp decline in new drug approval times (2). Despite this achievement, the total time to bring new products to market through the mid 1990s had not changed appreciably, due to the persistent rise in clinical develop-

ment seen over the last three decades (3,4).

Whereas PDUFA focused primarily on FDA's regulatory review procedures, the FDA Modernization Act of 1997 (5), which reauthorized the collection of user fees for an additional five years, contains provisions that specifically focus on how FDA can assist industry in shortening drug development times. These include restrictions on the amount of information FDA can require from a sponsor to initiate clinical research, the establishment of procedures for resolving scientific disputes between the agency and a sponsor, and FDA authorization to approve an NDA on the basis of one adequate and well-controlled clinical study in certain well-defined circumstances. Moreover, FDAMA required FDA to develop new procedures for holding formal meetings between the agency and sponsors, and established the "Fast Track Process" for speeding the development and approval of drugs that address unmet medical needs.

To gauge the impact of FDAMA's initiatives on the new drug development process, it is necessary to establish a baseline of development and approval times that covers a period preceding enactment of PDUFA and extends through the user fee era. In this report, we have examined average clinical development and approval times for new drugs approved during the 10-year period 1990 to 1999. These findings will serve as a benchmark for measuring the impact of FDAMA on FDA and drug industry performance, and for assessing the success of industry efforts to improve efficiency in the drug development process in the coming years.

METHODS

New drugs that were approved by the FDA during the 10-year period 1990 through 1999 and that met the Tufts Center for the Study of Drug Development's (Tufts CSDD's) definition of a new chemical entity (NCE) were used in the current analyses. An NCE is defined as any new molecular compound not previously approved in the United States, excluding diagnostic agents, vaccines, and

other biologic compounds not approved by FDA's Center for Drug Evaluation and Research (CDER). Also excluded are new salts, esters, and dosage forms of previously approved compounds. Included in the sample are a small number of recombinant proteins and biologics that were approved by CDER.

Data on each NCE were obtained from Tufts CSDD's annual survey of the pharmaceutical industry as well as from FDA and other public sources (eg, *Federal Register*, PhRMA bulletins and reports). When dates and figures from different sources did not agree, we used FDA and *Federal Register* data.

For each NCE, we calculated the lengths of the clinical development period (ie, clinical phase—time from the date of investigational new drug application [IND] filing to the date of new drug application [NDA] submission) and the regulatory review period (ie, approval phase—time from NDA submission to approval). In those cases where a sponsor resubmitted an application or submitted significant additional data subsequent to an NDA's filing, we used the original submission date in our analyses, despite the fact that this likely overestimates the total regulatory review period. On the other hand, for those NCEs that were subjects of a "rolling NDA" review process, that is, portions of the NDA were reviewed by FDA prior to the NDA's formal filing, we computed the approval phase based on the actual NDA submission date. In these cases, the approval phase likely underestimates the total regulatory review period by an unknown amount.

Mean clinical and approval phases were computed for all NCEs, as well as for NCEs grouped by priority rating and by therapeutic category, based on approved indication. In addition, mean lengths of clinical Phase I, Phase II, and Phase III were calculated based on the time from the start of each phase to the start of the next phase. Although this method does not account for gaps or overlap between clinical phases, it provides a reasonable measure of the time required to conduct sufficient clinical testing to justify continuation to the next clinical phase. It should be

noted that the sample sizes differ somewhat by clinical phase because in some cases the survey information on clinical phase dates was not complete.

We grouped NCEs into two five-year periods to compare clinical phase lengths and to examine development times by therapeutic category. This was done to ensure a sufficient number of data points in the sample to provide meaningful results.

RESULTS

Our data indicate that the approval phase for NCEs has declined markedly since implementation of PDUFA (Figure 1). While nearly constant at approximately two and one-half years during the early 1990s, the mean approval phase decreased 30% for the first two-year period for which NCEs subject to the user fee program constituted a substantial proportion of all approvals (1994–1995). The mean approval phase declined an additional 14% for the following two years and another 28% for the two most recent years. From the beginning to the end of the study period, the approval phase was shortened by approximately two years, representing a 58% decrease in average approval time.

The clinical phase first exhibits a downward trend later in the study period than is the case for the approval phase. After increasing 14% from the period 1990 to 1991 to the period 1994 to 1995, overall the mean approval phase decreased 17% for the 1996 to 1997 period and an additional 24% for the 1998 to 1999 period. On average, clinical development time for the most recent two-year period is 28% faster than for the initial period and 37% faster than for the period with the peak mean clinical phase (1994 to 1995).

Clinical and approval phases for priority rated (1P) and standard rated (1S) NCEs are presented in Table 1. Approval times for NCEs rated 1P decreased 53% over the study period, while approval times for drugs with a 1S rating fell 61%. Mean clinical development time for priority drugs is 48% lower for the most recent two-year period compared

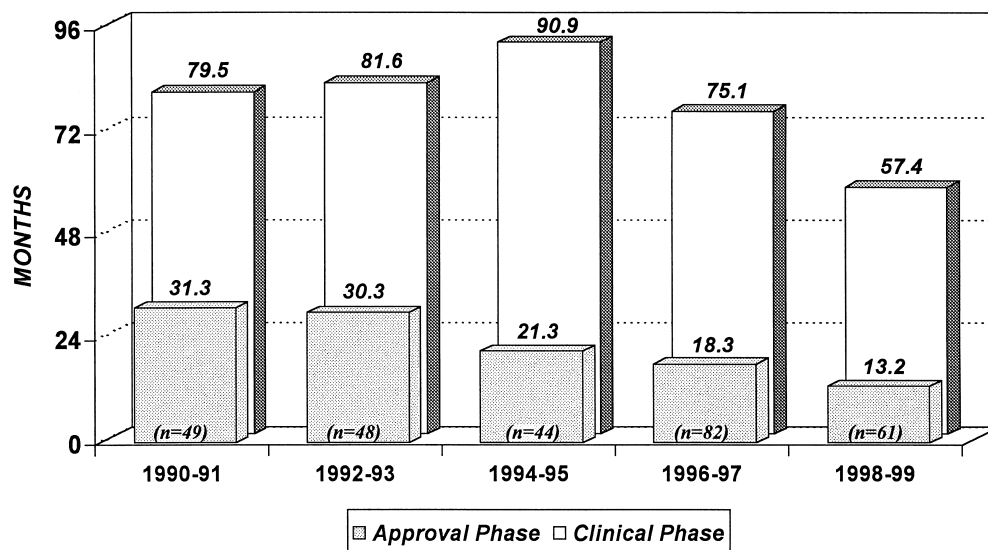


FIGURE 1. Mean clinical (IND filing to NDA submission) and approval (NDA submission to approval) phases for new chemical entities (NCEs) approved in five two-year periods from 1990 through 1999. Number of NCEs approved in each two-year period is indicated.

to the initial two-year period. On average, clinical development time for drugs with a standard rating declined 41% for the 1998 to 1999 period from a peak in the 1994 to 1995 period, but mean clinical development time for these drugs was somewhat longer (14%) in the 1998 to 1999 period than for the initial period.

Figure 2 presents the percentage of NCE approvals in a year that either had relatively

short approval phases (one year or less and six months or less) or had relatively long approval phases (two or more years), both pre- and post-PDUFA. The proportion of NCE approvals in the upper tail of the distribution of approval times (two or more years) exhibits a sharp decline following enactment of PDUFA, falling from 44% in 1993 to 3% in 1998 and 6% in 1999. Concomitant with the declines in the proportion of NCEs with

TABLE 1
Mean Clinical and Approval Phases for New Chemical Entities With Priority and Standard Ratings Approved in Five Two-Year Periods

	Clinical Phase		Approval Phase	
	Priority	Standard	Priority	Standard
1990–1991 (26; 23) [#]	103.2*	52.7	21.8	42.1
1992–1993 (23; 25)	102.8	62.1	20.6	39.2
1994–1995 (19; 25)	75.8	102.3	15.6	25.6
1996–1997 (24; 58)	81.8	72.9	13.3	20.4
1998–1999 (32; 29)	54.1	59.9	10.2	16.5

*All values given in months.

[#] Numbers in parentheses refer to the numbers of priority and standard approvals, respectively, in each two-year period.

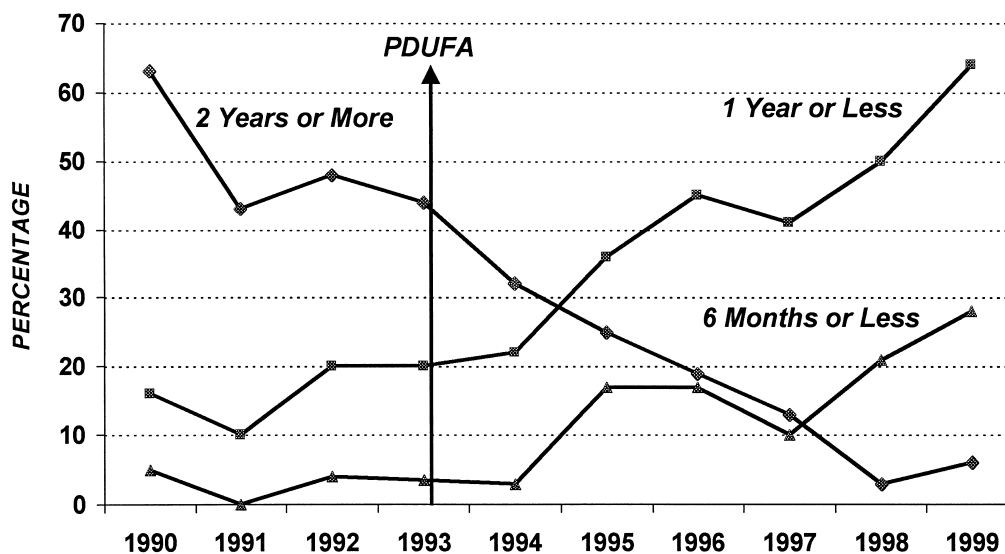


FIGURE 2. Percentage of NCEs approved during the period 1990 to 1999 with FDA approval times of two or more years, one year or less, and six months or less.

relatively long approval phases are increases in the proportions of NCEs that were approved quickly. However, substantial increases in the shares of approvals with relatively fast approval phases occur one year later. The percentage of NCE approvals with approval phases of one year or less increased from 22% in 1994 to 64% in 1999. The increase in the proportion of approvals with very fast approval times (six or fewer months from NDA submission) is even more notable, rising from 3% in 1994 to 28% in 1999.

The average lengths of the standard component clinical development phases for NCEs approved during two five-year periods are shown in Figure 3. Mean Phase I time increased 4.9 months (34%) from the first half of the 1990s to the second half. The mean length of Phase II increased 5.8 months (26%). However, mean Phase III time decreased 1.7 months (4%).

Changes in mean clinical phase from the first half of the 1990s to the second half varied substantially by therapeutic class. Four of the leading eight therapeutic classes show modest increases in average clinical phase between the two five-year periods,

while the other four classes show more substantial decreases (Figure 4). The average clinical phase increased 5%, 8%, 11%, and 12% for the CNS, endocrine, anesthetic/analgesic, and cardiovascular classes, respectively. However, mean clinical phase decreased 19%, 24%, 41%, and 44% for the AIDS antiviral, antiinfective, anticancer, and respiratory classes, respectively.

DISCUSSION

Previous Tufts CSDD studies have documented a steady rise in clinical development times over the past three decades (4). The current study highlights a reversal in this trend. The results presented here support and extend a recent Tufts CSDD report documenting a 19% decline in clinical development times from the three-year period 1993 to 1995 to the period 1996 to 1998 (3). In the current study, the mean clinical phase of 4.8 years for NCEs approved in the 1998 to 1999 period represents a 37% drop from the peak of 7.6 years seen in the 1994 to 1995 period.

The promising trend toward faster clinical

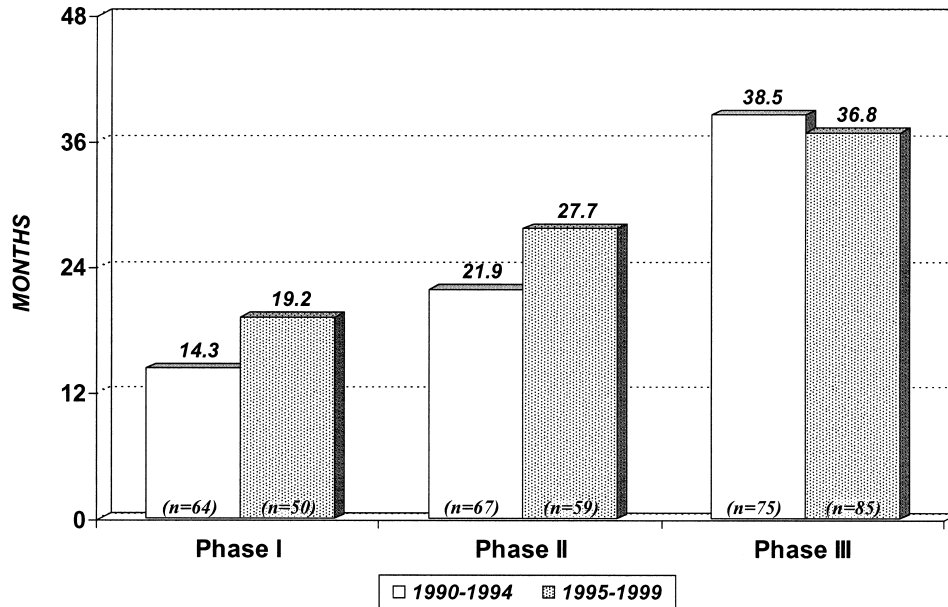


FIGURE 3. Mean clinical phase lengths for NCEs approved in two five-year periods. Clinical phase length is based on the time from the start date of a clinical phase to the start date of the subsequent clinical phase. Numbers of NCEs in each sample are indicated.

development times in the late 1990s is especially impressive in light of the dramatic growth in the size and complexity of clinical trials. This growth has occurred, in large part, due to the technical sophistication of newer products, advances in scientific knowledge leading to a better understanding of disease processes, an increase in the number of pharmacoeconomic and market-oriented studies conducted in the preregistration phase, and process inefficiencies within the drug industry.

There are several possible explanations for the decline in clinical development time observed in the current study. One possibility is that it reflects the impact of FDA's guidance and advice provided in formal meetings between the agency and drug sponsors. FDA/sponsor meetings held early in the development process have been shown to be associated with reduced clinical development times (6). FDA has recently revised its meeting procedures, offering drug sponsors faster agency response to requests for meetings, as

well as more efficient administrative procedures (7).

The current reduction in clinical development times may also reflect the impact of industry efforts to improve the efficiency of its drug development process. For example, many firms have stepped up efforts to identify and redesign or eliminate poorly designed clinical studies. Firms are also focusing on making better use of portfolio management to reduce late stage clinical failures and improve success rates (8). Some firms, in addition, are improving their clinical data management capabilities by implementing more efficient administrative procedures and by taking advantage of new computer-based technologies.

It is noteworthy that the overall reduction in clinical development times was not associated with overall reductions in standard clinical development phases. Whereas there was a modest reduction in Phase III length from the first half of the 1990s to the second half, Phase I and Phase II times increased over

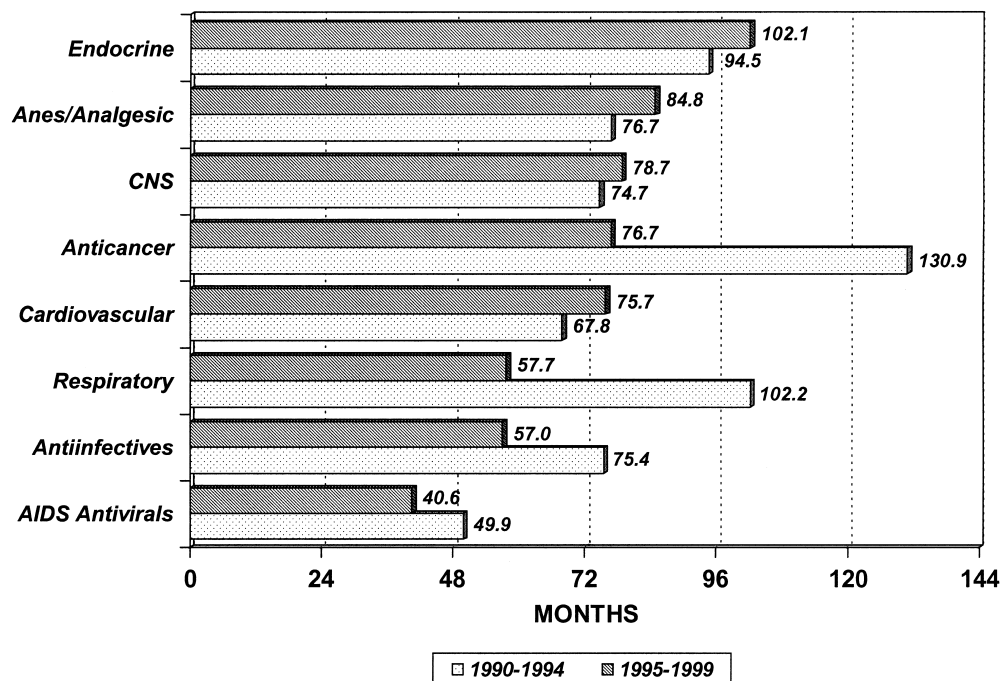


FIGURE 4. Mean clinical phase for NCEs approved in two five-year periods, grouped by therapeutic class. Therapeutic class groupings are based on the original, approved indication(s). Note that the antiinfective group excludes AIDS antiviral drug approvals.

the same period. The average phase lengths for approvals in the first half of the 1990s are very similar to those that we have reported elsewhere that were based on a sample of successful and unsuccessful investigational NCEs that resulted in United States approvals during the 1980s and early 1990s (9).

The increase in Phase I and Phase II lengths may reflect the greater number of pharmacodynamic/pharmacokinetic, dose-ranging, drug interaction, and market oriented studies now being conducted earlier in the clinical development process. In addition, in certain therapeutic classes, such as anticancer, some firms are compressing Phases I and II, leading to the reporting of longer Phase I times. Despite the observed increase in the lengths of Phase I and Phase II, the overall reduction in clinical development time suggests that efforts to better characterize the drug candidate early in the process are

largely successful in increasing overall efficiency and reducing development time.

While, in aggregate, clinical development times for recent approvals have declined, this trend is far from uniform when the data are analyzed at the therapeutic class level. Average clinical development times for a number of major therapeutic classes increased in recent years. These results suggest that substantial gains may still be possible from efforts to streamline the development process, at least for some types of compounds.

The change in the environment for pharmaceutical innovation in the United States that has occurred since passage of PDUFA has been nothing short of remarkable. Improved FDA review procedures and higher quality applications submitted by the drug industry have not only led to a dramatic reduction in NDA approval times, but also to an increase in the overall NDA approval rate,

and an increase in the number of NDAs approved on the first review (10,11). Moreover, the improved environment for drug development in the United States has led many firms to seek United States marketing approval for their product prior to obtaining foreign approval. The result is that there has been a substantial increase in the number of products that are first marketed in this country (3).

Many challenges remain for the research-based pharmaceutical industry, such as to further reduce lengthy discovery and development times, increase the number of products in development pipelines, reduce attrition rates, contain research and development costs, and develop breakthrough therapies (12). By continuing to focus on efficiency and by leveraging opportunities offered by regulatory initiatives and FDAMA, drug firms can achieve these goals. The analyses presented here allow us to assess the impact of current industry and agency efforts to accelerate new drug development and provide a framework for measuring the future impact of initiatives designed to improve the drug development process.

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