

# THE EFFECTS OF THE PRESCRIPTION DRUG USER FEE ACT AND THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT ON THE DEVELOPMENT AND APPROVAL OF THERAPEUTIC MEDICINES

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*The Prescription Drug User Fee Act of 1992 and the Food and Drug Administration Modernization Act of 1997 include provisions that were intended to increase the efficiency of the processes required for the clinical development and regulatory review of therapeutic medicines. The expected effects of the legislative acts were decreases in the time required for clinical development and product approval. Results from the analysis of the clinical (Investigational New Drug filing date to Biologic License Application [BLA]/New Drug Application [NDA] submission date) and approval (BLA/NDA submission date to approval date) phases for 54 applications for new biopharmaceutical products submitted to the Food and Drug Administration during fiscal years 1981 through 1998 indicate that while clinical phases consistently increased, the rate of increase slowed substantially for fiscal years 1997 through 1998. The approval phase for fiscal years 1997 through 1998, however, proved to be the shortest of any time period examined. Taken together, the data from fiscal years 1997 through 1998 show the first decrease in the mean total length of time required for clinical development and approval of biopharmaceuticals. Similar analyses of data for 384 applications for new chemical entities indicate that mean clinical and approval phase lengths were shorter for fiscal years 1997 through 1998 than for any other time period included in the study. The results of this study suggest that the regulatory reforms associated with enactment of PDUFA and FDAMA have had a marked effect on the development and approval of therapeutic medicines.*

**Key Words:** Prescription Drug User Fee Act; Food and Drug Administration Modernization Act; Biopharmaceutical; Drug development; Regulatory review

## INTRODUCTION

THE PROCESS OF pharmaceutical development and regulatory review has been, and

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Preliminary results were presented at the DIA 36th Annual Meeting, June 11–15, 2000, San Diego, California.

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will continue to be, greatly affected by two legislative acts passed in the 1990s: the Prescription Drug User Fee Act of 1992 (PDUFA) (1) and the Food and Drug Administration Modernization Act of 1997 (FDAMA) (2). A primary objective of both PDUFA and FDAMA was the improvement of the clinical development process and the Food and Drug Administration's (FDA's) review procedures. Since the development and approval of new thera-

peutics is actually a cooperative effort between FDA and sponsoring companies, the legislative acts have had an effect on how both FDA and the pharmaceutical industry operate.

The most important features of PDUFA were the establishment of user fees and FDA performance goals (3). The user fees, paid by the sponsoring companies starting in August 1993, were used to expand the staff needed to review Biologic License Applications and New Drug Applications and improve the FDA's administrative and information systems. The performance goals included the elimination of the existing backlog of overdue applications and specific timeline goals for the review of BLA/NDAs submitted for each fiscal year. To eliminate the backlog, FDA agreed to review applications pending as of October 1, 1992 within 24 months of the initiation of user fee payments. The performance goals initially applied to all applications regardless of review status and were defined differently for each fiscal year. The review process was separated into a phase for FDA to review and act on an original application (first action phase), and, if necessary, subsequent review phases of the resubmitted application (second action phase, third action phase, etc.). The goals set included a first action phase of 12 months for a percentage of all applications submitted in a given fiscal year, referred to as a fiscal year cohort, starting in 1994 (55% in fiscal year 1994, 70% in fiscal year 1995, 80% in fiscal year 1996). Starting in 1997, separate goals for the first action phase were applied to standard review products (12 months for 90% of the fiscal year cohort) and priority review products (6 months for 90% of the fiscal year cohort). The goal of six months for the time to review each resubmission was phased in over fiscal years 1994 through 1997 in a similar fashion. PDUFA was renewed and amended by FDAMA in November 1997.

While PDUFA primarily addressed the major issue of timely review of BLAs and NDAs, FDAMA was designed to facilitate the process of clinical development. Sections of FDAMA establish fast track designation,

mandate the formation of a publicly-accessible clinical trials database, allow the abbreviated reporting of data and the use of a single, well-controlled trial to establish efficacy, and clarify requirements for investigational new drug applications as well as BLAs, NDAs, and postmarketing studies (4). Timeline performance goals were also included in FDAMA; the new goals build on the ones set in PDUFA. For original applications, the goal of a first action phase of six months for 90% of priority applications submitted each fiscal year was maintained, and the goal of a first action phase of 10 months for 90% of standard applications was phased in (30% in fiscal year 1999, 50% in fiscal year 2000, 70% in fiscal year 2001, and 90% in fiscal year 2002). Under FDAMA, resubmitted applications were designated as class 1 (applications with limited, defined deficiencies) or class 2 (applications with deficiencies outside the scope of the definition for class 1). The performance goals for class 2 resubmissions were constant (6 months for 90% of the cohort), while the performance goals for class 1 resubmissions started at two months for 30% of fiscal year 1998 cohort and gradually became more stringent (2 months for 90% of the fiscal year 2002 cohort).

Taken together, the provisions of PDUFA and FDAMA were intended to increase efficiency in both clinical development and regulatory review and, therefore, reduce the time required for these stages in the overall process of gaining marketing approval for therapeutic medicines. The data presented here suggest that, as implemented to date, PDUFA and FDAMA have been effective in achieving this goal.

## METHODS

This study presents analyses of the clinical development and regulatory review of new biopharmaceuticals and New Chemical Entities (NCEs) that were reviewed by the FDA during fiscal years 1981 through 1998. BLAs or NDAs for products included here were submitted during fiscal years 1981 through 1998; marketing approvals for these products

were issued during fiscal years 1982 through 1999. The fiscal year for each year included in this study, with the exception of fiscal years 1992 and 1993, included October 1 through September 30; fiscal year 1992 included October 1, 1991 through August 31, 1992, and fiscal year 1993 included September 1, 1992 through September 30, 1993 (5).

A new biopharmaceutical was defined as the first unique therapeutic biopharmaceutical product approved for any indication. Identical products approved subsequently were not included, with the exception of the first recombinant version of an approved nonrecombinant protein. Diagnostic monoclonal antibodies, vaccines (with the exception of recombinant vaccines), and biopharmaceutical products approved for supplemental indications were not included. A total of 54 BLAs/NDAs submitted to FDA during fiscal years 1981 through 1998 were for products that fit the definition of a new biopharmaceutical; 30 of these were submitted during fiscal years 1993 through 1998.

An NCE was defined as any new molecular compound not previously approved in the United States, excluding diagnostic agents, vaccines, biopharmaceuticals, and new salts, esters, and dosage forms of previously approved compounds. A total of 384 NDAs submitted to FDA during 1981 through 1998 were for products that fit the definition of a NCE; 147 of these were submitted during fiscal years 1993 through 1998.

Biopharmaceutical products were reviewed at either the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER). CBER first accepted BLAs in May 1996; prior to that time a product license application (PLA) and an establishment license application (ELA) were required for each new product. BLAs and PLA/ELAs were considered to be equivalent for this study, and the term BLA was used to refer to both types of submissions. All NCEs included in this study were reviewed by CDER.

Product review phases for BLA/NDAs submitted to FDA during fiscal years 1993 through 1998 were described using the fol-

lowing terms: first action phase, total FDA phase, and approval phase. The first action phase was defined as the time required by the FDA to review and act on a BLA/NDA submission. Specifically, the first action phase was the time between the BLA/NDA submission date and the date of the action letter indicating that the application was approved, approvable, not approvable, or required additional information (complete response letter). The total FDA phase was defined as the sum of the time required for all action phases (first action and all subsequent FDA actions resulting from resubmissions of the product application). The approval phase was defined as the sum of the total FDA time and the total sponsor response time (total elapsed time between dates of action letters and dates of resubmitted applications), which was also equivalent to the time between the BLA/NDA submission date and the approval date.

Since values such as FDA action times and sponsor response times were not reported publicly for BLA/NDAs submitted prior to 1993, mean clinical, approval, and total phases were used to compare the data for prefiscal year 1993 BLA/NDA submissions with the data for fiscal years 1993 through 1998 BLA/NDA submissions. The clinical phase was defined as the time between the date the investigational new drug application was filed with the FDA and the date of the submission of the BLA/NDA. The approval phase was defined as above (time between the BLA/NDA submission and FDA approval dates). The total phase was defined as the time between the dates of the IND filing and FDA approval.

Data for products included in this study were collected through surveys of the sponsoring companies and from publicly accessible documents (5–11). Tufts Center for the Study of Drug Development maintains databases of medicinal products that entered human clinical trials from the early 1960s to the present. The databases include information on the development and regulatory review of products currently in development, terminated products, and FDA-approved products.

## RESULTS

### Action Phase Success Rates: Fiscal Year Cohorts 1993 through 1998

A total of 30 new biopharmaceutical BLAs or NDAs were submitted to the FDA during fiscal years 1993 through 1998 and approved during fiscal years 1993 through 1999. The specific outcome of each of the actions for the group of 30 products, as shown as percentages, is presented in Table 1. Of the total, less than half were approved by the first action. For the applications that were not approved by the first action, roughly equivalent numbers were approvable, not approvable, or required additional information for review (complete response). For subsequent actions, the percentage of applications approved increased as the sponsoring companies addressed the deficiencies in the applications successfully. One application of the group of 30 required a fourth action for approval.

The success rates for the biopharmaceuticals were consistent during the time period fiscal years 1993 through 1998. In contrast, the success rates for the NCEs were distinctly different for applications submitted during fiscal years 1993 through 1995 (Table 2) compared with those submitted during fiscal years 1996 through 1998 (Table 3). A larger percentage of applications submitted during fiscal years 1996 through 1998 were approved by the first action and a smaller percentage were not approvable compared with those submitted during fiscal years 1993 through 1995 (59% vs. 37% and 1% vs. 16%, respectively). The percent of applications approved by second and third actions was also

larger for applications submitted during fiscal years 1996 through 1998 compared with those submitted during fiscal years 1993 through 1995.

### Review Phases: Fiscal Year Cohorts 1993 through 1998

Review phases for 30 new biopharmaceutical BLA/NDAs submitted during fiscal years 1993 through 1998 were calculated and the mean values for each fiscal year are shown in Table 4. No distinction was made between priority and standard reviewed products prior to fiscal year 1997 because FDA's performance goals do not specify separate goals until fiscal year 1997. The mean first action phase decreased between fiscal year 1993 and fiscal year 1994, but remained near the goal of a 12-month review for fiscal year 1995 and fiscal year 1996. The first action phase was 15 months for one product in each of fiscal years 1995 and 1996 (deadline extended by 3 months due to submission of a major amendment within 3 months of the action due date), thus, the mean first action phase is slightly elevated for those years. In fiscal year 1997 standard-review products received a first action in a mean time of 11.5 months, compared with 7.0 months for priority review products. The mean first action phase for the priority review products decreased by 20% when the values for fiscal year 1997 are compared with fiscal year 1998. All BLA/NDAs submitted in fiscal year 1998 for new biopharmaceutical products were priority reviewed. The mean total FDA phase decreased from fiscal year 1993

**TABLE 1**  
**New Biopharmaceuticals: Fiscal Years 1993 through 1998**  
**Cohort Action Phase Success Rates**

|                   | 1st Action<br>(n = 30) | 2nd Action<br>(n = 16) | 3rd Action<br>(n = 5) | 4th Action<br>(n = 1) |
|-------------------|------------------------|------------------------|-----------------------|-----------------------|
| Approved          | 47%                    | 69%                    | 80%                   | 100%                  |
| Approvable        | 17%                    | 6%                     | 0%                    | 0%                    |
| Not Approvable    | 20%                    | 6%                     | 0%                    | 0%                    |
| Complete Response | 17%                    | 19%                    | 20%                   | 0%                    |

**TABLE 2**  
**NCEs: Fiscal Years 1993 through 1995**  
**Cohort Action Phase Success Rates**

|                   | <b>1st<br/>Action<br/>(n = 68)</b> | <b>2nd<br/>Action<br/>(n = 43)</b> | <b>3rd<br/>Action*<br/>(n = 9)</b> |
|-------------------|------------------------------------|------------------------------------|------------------------------------|
| Approved          | 37%                                | 79%                                | 89%                                |
| Approvable        | 47%                                | 17%                                | 0%                                 |
| Not<br>Approvable | 16%                                | 2%                                 | 11%                                |

\*One NCE required a total of 6 actions; only results through the 3rd actions are shown for this product.

through fiscal year 1994, but there was a steady increase during fiscal years 1995 and 1996. The upward trend was reversed in fiscal year 1997 when the mean total FDA phase decreased to 14.7 months for standard review products and 8.9 months for priority review products. Compared with fiscal year 1997 priority review products, there was a 27% decrease in the mean total FDA phase in fiscal year 1998. The pattern observed in the values for the mean approval phase, which includes the sponsor response time, is similar to that seen for the total FDA phases, that is, an increase to a peak in fiscal year 1996 followed by a decrease in the values. The fiscal year 1993 mean approval phase (23.6 months), the longest observed for any fiscal year in the period fiscal years 1993 through 1998, was due to a long mean sponsor response time (10.6 months). The range of sponsor response time as a percentage of the approval phase was 1% to 14% during fiscal years 1994 through 1998.

**TABLE 3**  
**NCEs: Fiscal Years 1996 through 1998**  
**Cohort Action Phase Success Rates**

|                   | <b>1st<br/>Action<br/>(n = 79)</b> | <b>2nd<br/>Action<br/>(n = 32)</b> | <b>3rd<br/>Action<br/>(n = 2)</b> |
|-------------------|------------------------------------|------------------------------------|-----------------------------------|
| Approved          | 59%                                | 94%                                | 100%                              |
| Approvable        | 38%                                | 6%                                 | 0%                                |
| Not<br>Approvable | 1%                                 | 0%                                 | 0%                                |
| Withdrawn         | 1%                                 | 0%                                 | 0%                                |

The mean review phases for NCE applications submitted during fiscal years 1993 through 1998 are shown in Table 5. The first action phase decreased consistently during fiscal years 1993 through 1996. Comparing standard and priority applications submitted in fiscal year 1997 to those submitted in fiscal year 1998, there was a 2% and a 5% reduction in the mean first action phase, respectively. The mean total FDA phase and approval phases also decreased during fiscal years 1993 through 1996 but there was an increase in both phases for standard review NCEs applications submitted during fiscal year 1997 compared with those submitted in fiscal year 1998 (10% and 12%, respectively). In contrast, there was a decrease of 19% in the mean total FDA phase and 30% in the mean approval phase for priority review NCE applications submitted during fiscal year 1997 compared with fiscal year 1998. For the NCE applications, the range of sponsor response time as a percentage of the approval phase was 4% to 20% during fiscal years 1993 through 1998.

**Clinical, Approval, and Total Phases:  
 Fiscal Year Cohorts 1981 through 1998**

To assess the impact of PDUFA and FDAMA on the length of time required to develop and gain approval for new therapeutic medicines, the clinical, approval, and total phases were calculated for BLA/NDAs submitted from fiscal year 1981 through fiscal year 1998. Fiscal year 1981 was selected as the start of the time period because the first BLA for a recombinant protein was submitted during that year. The results were grouped by fiscal year as follows: fiscal years 1981 through 1985, fiscal years 1986 through 1989, fiscal years 1990 through 1993 (fiscal years 1990 through 1993 had no review performance goal), fiscal years 1994 through 1996 (review performance goal increased from 55% to 80% of original applications reviewed in 12 months during fiscal years 1994 through 1996), and fiscal years 1997 through 1998 (the review performance goal was the same for both fiscal years).

**TABLE 4**  
**New Biopharmaceuticals: Mean Review Phases for Each**  
**Fiscal Year Cohort 1993 through 1998**

|                                   | <b>1st Action<br/>Phase (months)</b> | <b>Total FDA<br/>Phase (months)</b> | <b>Approval<br/>Phase (months)</b> |
|-----------------------------------|--------------------------------------|-------------------------------------|------------------------------------|
| Fiscal Year 1993 (n = 5)          | 9.1                                  | 13.0                                | 23.6                               |
| Fiscal Year 1994 (n = 1)          | 6.0                                  | 10.5                                | 12.2                               |
| Fiscal Year 1995 (n = 3)          | 12.9                                 | 14.1                                | 14.3                               |
| Fiscal Year 1996 (n = 4)          | 11.0                                 | 16.8                                | 19.6                               |
| Fiscal Year 1997 Standard (n = 5) | 11.5                                 | 14.7                                | 15.9                               |
| Fiscal Year 1997 Priority (n = 5) | 7.0                                  | 8.9                                 | 9.8                                |
| Fiscal Year 1998 Priority (n = 7) | 5.6                                  | 6.5                                 | 7.0                                |

The results for 54 new biopharmaceutical BLA/NDAs submitted from fiscal year 1981 through fiscal year 1998 are shown in Figure 1. The mean clinical phase increased in each subsequent time period by 38%, 30%, 32%, and 4%, respectively. The opposite trend prevailed for the mean approval phase, where a decrease was observed in each subsequent time period. The mean total phase increased by 4%, 14%, and 16% in subsequent time periods including fiscal years 1994 through 1996. The trend was reversed however, during the fiscal years 1997 through 1998 time period. For the first time, a decrease (of 5%) in the mean total phase was observed.

The results for 384 NCE applications submitted in fiscal years 1981 through 1998 are shown in Figure 2. The mean clinical phase increased by 19% in fiscal years 1986 through 1989 compared with fiscal years

1981 through 1985 but remained relatively constant in fiscal years 1994 through 1996. A decrease of 21% was observed in fiscal years 1997 through 1998 compared with fiscal years 1994 through 1996. As was the case with the new biopharmaceuticals, the mean approval phase of the NCEs decreased in each of the subsequent time periods. The overall trend, as evidenced by the mean total phase data, was an increase of 11% during fiscal years 1986 through 1989 compared with fiscal years 1981 through 1985 but a decrease in the total phase for each subsequent time period (7%, 9%, and 21% for the time periods fiscal years 1990 through 1993 compared with fiscal years 1986 through 1989, fiscal years 1994 through 1996 compared with fiscal years 1990 through 1993, and fiscal years 1997 through 1998 compared with fiscal years 1994 through 1996, respectively).

**TABLE 5**  
**NCEs: Mean Review Phases for Each Fiscal Year Cohort 1993 through 1998**

|                                    | <b>1st Action<br/>Phase (months)</b> | <b>Total FDA<br/>Phase (months)</b> | <b>Approval<br/>Phase (months)</b> |
|------------------------------------|--------------------------------------|-------------------------------------|------------------------------------|
| Fiscal Year 1993 (n = 15)          | 13.9                                 | 16.6                                | 20.3                               |
| Fiscal Year 1994 (n = 22)          | 12.4                                 | 14.9                                | 18.0                               |
| Fiscal Year 1995 (n = 31)          | 11.0                                 | 14.4                                | 17.1                               |
| Fiscal Year 1996 (n = 37)          | 9.8                                  | 10.9                                | 11.8                               |
| Fiscal Year 1997 Standard (n = 19) | 12.1                                 | 13.0                                | 13.6                               |
| Fiscal Year 1997 Priority (n = 7)  | 6.3                                  | 8.5                                 | 10.7                               |
| Fiscal Year 1998 Standard (n = 5)  | 11.8                                 | 14.3                                | 15.3                               |
| Fiscal Year 1998 Priority (n = 11) | 6.0                                  | 6.9                                 | 7.5                                |

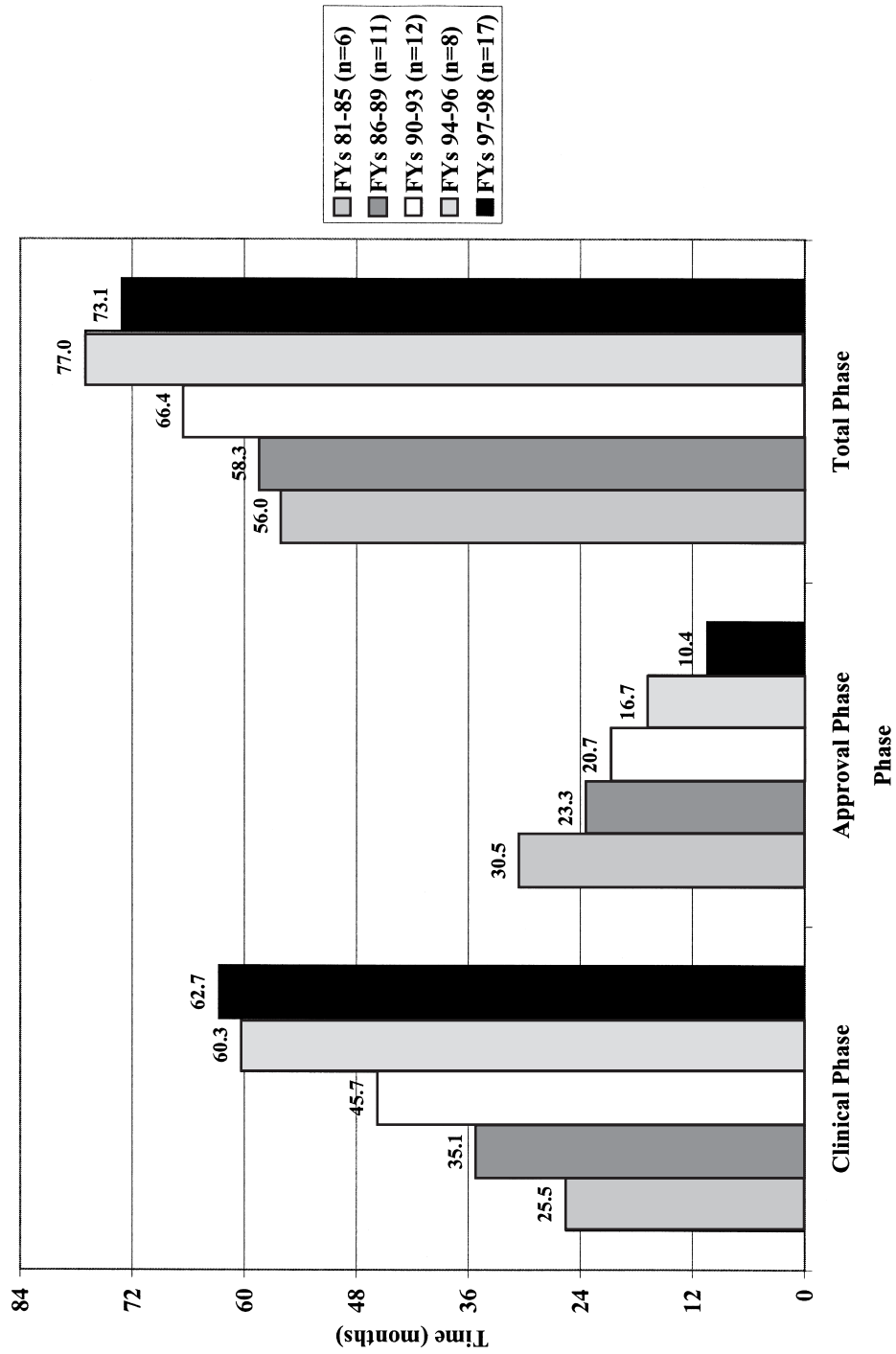


FIGURE 1. New biopharmaceuticals: Mean clinical, approval, and total phases for cohorts in fiscal years 1981 through 1998.

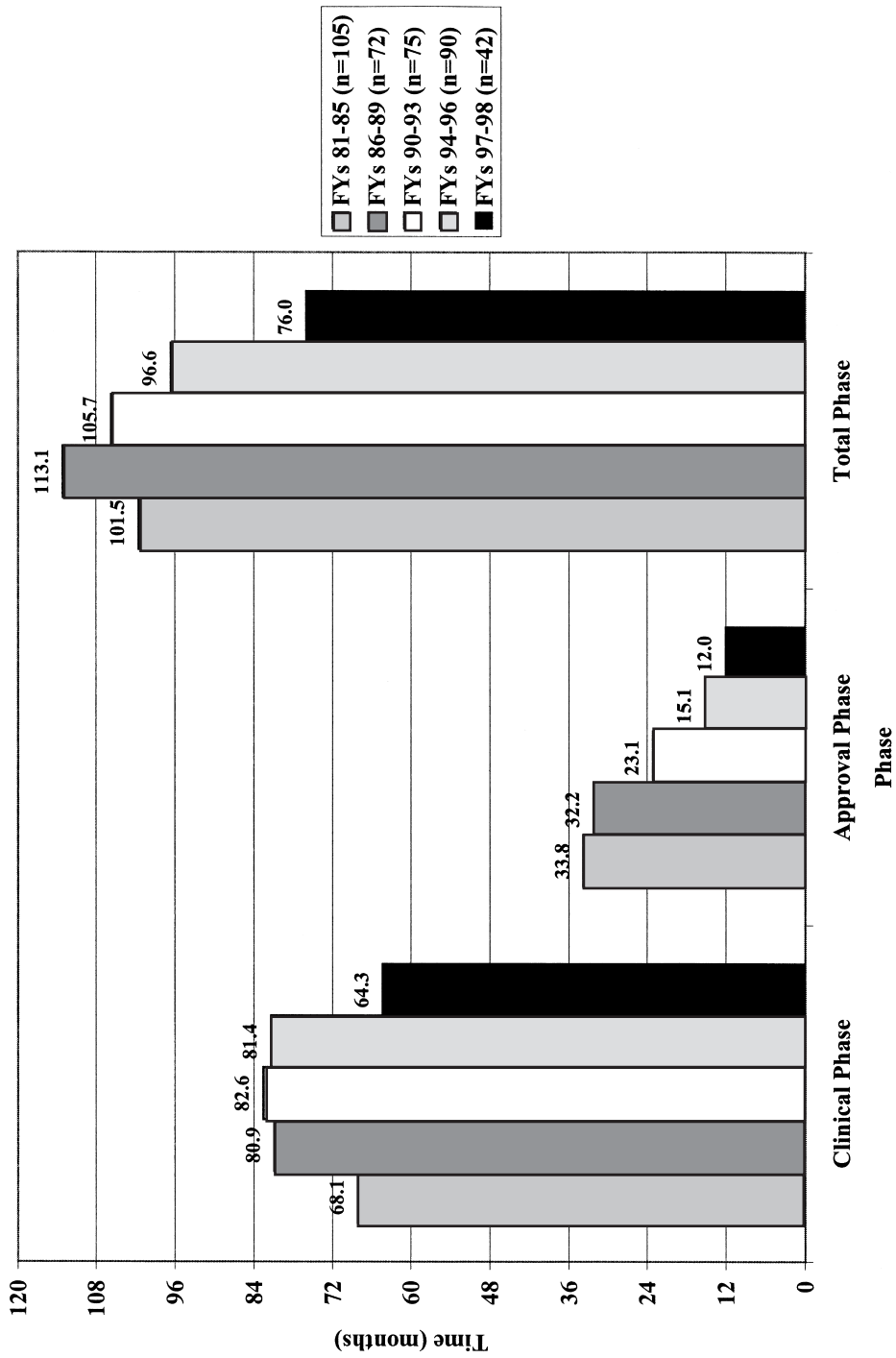


FIGURE 2. NCEs: Mean clinical, approval, and total phases for cohorts in fiscal years 1981 through 1998.

## DISCUSSION

PDUFA and FDAMA were designed to have beneficial effects on the processes by which therapeutic medicines are developed and approved. The intended effects included improved communication between FDA and industry, and faster clinical and approval phases. The evaluation of action phase success rates for fiscal years 1993 through 1998 submissions suggests that the pharmaceutical industry developed a better understanding of the requirements for successful NDAs for therapeutic medicines over the time period. This is clearly demonstrated by the improvement in the action phase success rates of the NCE applications submitted during fiscal years 1996 through 1998 compared with those submitted during fiscal years 1993 through 1995. The biopharmaceutical industry appears to be lagging behind traditional pharmaceutical firms in this area. This may be because, overall, the biopharmaceutical industry has less experience with the development and approval process—far more NCEs are approved in any given fiscal year compared with biopharmaceuticals (biopharmaceuticals made up 14% of the total number of therapeutics included in this study). Also, the development of biopharmaceuticals holds additional challenges in the areas of characterization and consistent manufacturing of products, which adds to the complexity of the review of these products compared with traditional drugs.

The performance goals for the review of BLAs/NDAs were an important part of both PDUFA and FDAMA. The data suggest that FDA's attempts to achieve these goals have been successful. The goals apply to the entire cohort of any given fiscal year, thus the absolute determination of whether the goals have been met cannot be made by analysis of a subset of the cohort, as was done for this study. Nevertheless, the data show that the first action phase has decreased over time for both the biopharmaceuticals and the NCEs and has been at or near the goal for each of fiscal years 1994 through 1998. Sponsor response times have decreased over the fiscal

years 1993 through 1998 time period. Shorter sponsor response times suggest that sponsor companies and FDA are communicating more effectively.

The effects of the legislative acts were expected to be most apparent when the clinical, approval, and total phases of the pre-PDUFA period (fiscal years 1981 through 1993; performance goals were not implemented until fiscal year 1994) were compared with the post-PDUFA period (fiscal years 1994 through 1998). For both biopharmaceuticals and NCEs, the effects became clear during the fiscal years 1997 through 1998 time period. Clinical phases for the biopharmaceuticals consistently increased over fiscal years 1981 to 1998, though the rate of increase was only 4% between fiscal years 1994 through 1996 and fiscal years 1997 through 1998. The approval phase consistently decreased over each of the time periods. A significant decrease (24%) occurred between fiscal years 1981 through 1985 and fiscal years 1986 through 1989. FDA was undergoing a significant reorganization during this period, including the establishment of CBER and CDER as separate entities, which may have contributed to the observed decrease. The largest decrease (38%) was between fiscal years 1994 through 1996 and fiscal years 1997 through 1998. The net result of the trends in the clinical and approval phases for biopharmaceuticals was a consistent increase in the total phase for the fiscal years 1981 through 1996 cohorts but for the first time, a decrease for the fiscal years 1997 through 1998 cohort.

Trends in the clinical and approval phases for NCEs were slightly different but the net result was the same—the effects of PDUFA and FDAMA were evident in the results for the fiscal years 1997 through 1998 cohort. Compared with the fiscal years 1994 through 1996 cohort, a 21% reduction in the clinical phase and a 20% reduction in the approval phase resulted in a 21% decrease in the total phase. The total phase length for the fiscal years 1997 through 1998 cohort of NCEs applications was the shortest of all of the time periods included in the study.

The results presented suggest that the provisions included in PDUFA and FDAMA have been successful in reducing development and approval times for therapeutic medicines. Reviews have been done in a timely manner and approval phases for both biopharmaceuticals and NCEs have decreased dramatically between the time periods of fiscal years 1981 through 1984 to fiscal years 1997 through 1998. Because there is some minimum amount of time necessary to ensure an adequate review of BLA/NDAs, review times are not likely to decrease significantly in the future. The greater emphasis on communication between industry and FDA and clarification of the requirements for clinical development suggest that additional decreases in clinical phases may occur, however. Provisions in the legislation that will renew and amend FDAMA (due in 2002) are likely to have further effects on the process of development and approval of therapeutic medicines. Tufts CSDD will continue to track and report on these effects in future studies.

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*Acknowledgments*—The authors gratefully acknowledge colleagues at Tufts CSDD for comments and suggestions on the manuscript.

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