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Report to the Chairman, Committee on Health, Education, Labor, and Pensions, U.S. Senate

September 2002

FOOD AND DRUG ADMINISTRATION

Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities

GAO-02-958

Contents

Abbreviations

BIO	Biotechnology Industry Organization
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act of 1997
FTE	full-time equivalent
HHS	Department of Health and Human Services
NDA	new drug application
NIH	National Institutes of Health
NME	new molecular entity
OPM	Office of Personnel Management
PDUFA	Prescription Drug User Fee Act
PhRMA	Pharmaceutical Research and Manufacturers of America

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United States General Accounting Office
Washington, DC 20548

September 17, 2002

The Honorable Edward M. Kennedy
Chairman
Committee on Health, Education,
Labor, and Pensions
United States Senate

Dear Mr. Chairman:

Ten years ago, the Congress passed the Prescription Drug User Fee Act (PDUFA)[1] to provide additional resources for the Food and Drug Administration (FDA) to speed up the process of reviewing applications for new drugs and biological products.[2] FDA is responsible for ensuring that all such products are safe and effective. Under PDUFA, FDA collects user fees from the pharmaceutical and biotechnology industries to supplement its annual appropriation for salaries and expenses. PDUFA requires FDA to use the additional funds for the review of applications. The original act was set to expire in 1997, but the FDA Modernization Act of 1997 (FDAMA) extended the PDUFA user fee program for an additional 5 years.[3] The Prescription Drug User Fee Amendments of 2002 extended PDUFA for 5 more years, effective October 1, 2002.[4]

As FDA endeavors to reduce its review time under the user fee program, concerns have been raised about the effects the program may be having on the resources available to other FDA programs, which set and enforce safety standards for such products as medical devices, blood products, cosmetics, and all foods except for meat and poultry. Concerns have also been raised about the effects of the expedited process on FDA staff involved in the review process. In addition, some consumer and patient

[1]P.L. 102-571, Title I, §103.

[2]Biological products, or biologics, are derived from living sources (such as humans, animals, and microorganisms) as opposed to being chemically synthesized.

[3]P.L. 105-115, Title I, §103.

[4]The Prescription Drug User Fee Amendments of 2002 were included in Title V of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, P.L. 107-188.

groups have noted the removal of several drugs from the market in recent years and expressed concern that PDUFA's emphasis on faster review times may have compromised drug safety.

To assist the committee in its consideration of PDUFA's reauthorization, you asked us to evaluate the prescription drug user fee program. On May 15, 2002, we briefed your staff on the results of our work. This report provides a more detailed discussion of those results. Specifically, you asked us to examine (1) how PDUFA has affected the funding and approval times for FDA's review of new drug and biologic applications, (2) whether PDUFA has had an effect on the funding and operation of FDA's non-PDUFA activities, (3) whether the workload, attrition, and professional development of FDA reviewers have changed since the user fee program was reauthorized in 1997, and (4) how the rate of drug withdrawals from the market has changed since PDUFA was enacted in 1992 and what actions are being taken by FDA to monitor adverse drug effects.

To examine these issues, we reviewed and analyzed FDA reports, data, and other agency documents and interviewed FDA officials from the Office of the Associate Commissioner for Planning, the Centers for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER). In this report, we will refer to the original act passed in 1992 as PDUFA I, the amendments of 1997 as PDUFA II, and the Prescription Drug User Fee Amendments of 2002 as PDUFA III. Unless specified, where we discuss PDUFA, we are referring to the period from 1992 through September 2002. We also reviewed and analyzed federal employment data from the Office of Personnel Management (OPM). We interviewed representatives from the trade associations that represent companies that pay user fees, the Pharmaceutical Research and Manufacturers of America (PhRMA), and the Biotechnology Industry Organization (BIO), and reviewed and analyzed information that they provided. In addition, we attended an FDA stakeholders' meeting that included industry and consumer groups and reviewed documents prepared by the Consumer Federation of America, Public Citizen, and others. Due to time constraints, we were unable to independently verify the accuracy of all data provided. Apart from this exception, our work was conducted from August 2001 through July 2002 in accordance with generally accepted government auditing standards.

Results in Brief

PDUFA has been successful in providing FDA with the funding necessary to hire additional drug reviewers, thereby making new drugs available in the United States more quickly. Approval times have declined for both priority drugs, those that FDA expects to provide significant therapeutic benefits beyond drugs already marketed, and standard drugs, those for which there are no perceived significant therapeutic benefits beyond those for available drugs. From 1993 to 2001, the median approval time for new drug applications for standard drugs dropped from 27 months to 14 months. The median approval time for new drug applications for priority drugs has remained stable at 6 months since 1997. However, the approval time for standard new molecular entities (NME), drugs containing active ingredients that have never been marketed in the United States in any form, has increased since 1998 from about 13 months to 20 months. In contrast, median approval times for new biologic applications have fluctuated since 1993, ranging from a low of 12 months in 1997 to a high of about 32 months in 1995. In 2001, the median approval time for biologic applications was about 22 months.

While PDUFA has increased the funds available for FDA's drug and biologic review activities, funds for non-PDUFA activities, such as regulating foods and medical devices, have constituted a smaller portion of FDA's total budget. According to FDA officials, two factors may have contributed to the reduced share of FDA funds allocated to other activities. First, to satisfy the minimum allocation of funds required by PDUFA, FDA had to continually increase the amount of appropriated funds allocated to drug and biologic reviews. Moreover, FDA's difficulty in determining the amount spent to meet this requirement has resulted in the agency exceeding the spending baseline from 3 to 10 percent in 7 of the 9 years since PDUFA. Second, from fiscal year 1994 through fiscal year 2001, annual appropriations for the agency did not include the costs of pay raises for its employees, according to FDA officials. FDA reduced the resources spent on other activities to fund these pay raises.

PDUFA II has resulted in increased reviewer workload and may be contributing to decreased training and development and increased attrition among FDA's staff responsible for reviewing new drugs and biologics. PDUFA II affected reviewer workload by shortening review times and establishing new performance goals to reduce overall drug development times. Also, FDA's attrition rates for most of the scientific occupations involved in its drug review process are higher than those for comparable occupations in other federal public health agencies and the remainder of the federal government.

Our analysis of FDA data found that a higher percentage of drugs has been withdrawn from the market for safety-related reasons since PDUFA's enactment than prior to the law's enactment, but that the size of the increase in drug withdrawal rates differs depending on the period examined. The share of more recently approved drugs (1997 to 2000) that have been withdrawn has risen to 5.34 percent, from 1.56 percent in the period immediately after PDUFA's implementation (1993 to 1996). When withdrawal rates are compared for the 8-year periods before and after PDUFA, the increase is from 3.10 to 3.47 percent. Drug withdrawals have been affected by several factors. For example, some drugs were removed from the market because doctors and patients did not use them correctly, while other drugs were found to have rare side effects that were not detected in clinical trials. The increased rate of drug withdrawals suggests the need for FDA to strengthen its postmarket surveillance activities. FDA plans to spend about $71 million in user fees over the next 5 years to better monitor the safety of new drug products once they have reached the market and track adverse effects from marketed drugs.

In technical comments on a draft of this report, FDA disagreed with our analyses and discussion of drug withdrawal rates. FDA officials said that our analysis of drug withdrawals for the 8-year period preceding PDUFA versus the first 8 years of PDUFA does not show any real increase, and that our analysis using the 4-year groupings was significantly affected by the small number of withdrawals during each period. While we agree that the small number of withdrawals in any given year may affect the variation in the withdrawal rate, we believe that our analyses are appropriate and both analyses show an increase in the withdrawal rates since PDUFA's implementation. Under PDUFA III, FDA will be able to use user fees for additional drug safety activities that could not be funded by PDUFA I and II. We incorporated FDA's other technical comments as appropriate.

Background

Over the past two decades, extensive research and development have led to new prescription drug therapies and improvements over existing therapies, and the number of prescription drugs on the market has increased dramatically. Some of these therapies can at times replace other health care interventions,[5] and as a result, the importance of prescription drugs as part of health care has grown. Consequently, Americans are using

[5]For example, cholesterol-lowering drugs may obviate the need for angioplasty, that is, a surgical procedure to remove cholesterol plaque on the inside wall of a blood vessel.

a greater number of pharmaceuticals than ever before. According to the National Institute for Health Care Management, pharmacists dispensed 3.1 billion prescriptions in the United States in 2001, up from 1.9 billion in 1992 and 2.4 billion in 1997.[6]

FDA's Drug and Biologic Review Process

In addition to ensuring that new drugs and biologics are safe and effective[7] and that applications for their approval are reviewed timely, FDA is also responsible for monitoring drugs and biologics for continued safety after they are in use. Within FDA, CDER and CBER are responsible for reviewing applications for new drugs and biologics, respectively. The centers also are responsible for reviewing efficacy supplements, manufacturing supplements, labeling supplements, and investigational new drugs. Efficacy supplements are applications for new or expanded uses of already approved products, including addition of a new indication, a change in the dosing regimen such as increase or decrease in daily dosage, or a change in the patient population. Manufacturing supplements to new drug applications are used to notify the centers in advance of certain drug manufacturing changes. Investigational new drug applications are submitted for new drugs or new indications for already approved drugs that are to be used in clinical investigations.

The review process for both centers requires evaluating scientific and clinical data submitted by manufacturers to determine whether the products meet the agency's standards for approval. The first decision a center must make in its review process is whether to accept a new drug application (NDA) or biologics license application (BLA). FDA can issue one of several action letters. If the application is not sufficiently complete to allow a substantive review, the center issues a "refuse-to-file" letter. Once the center has accepted the application, it designates the product as either "priority," for products that would provide significant therapeutic gains compared to any existing products on the market, or "standard," for products that would provide no significant therapeutic advantage over other drugs already on the market. After a thorough assessment of the

[6]IMS Health, "National Prescription Audit and NDCHealth's Source DataBase and Pharmaceutical Audit Suite," *Prescription Drug Expenditures in 2001: Another Year of Escalating Costs*, (Washington, D.C.: National Institute for Health Care Management, May 2002).

[7]In order to be licensed, biologics must be safe, pure, and potent. 42 U.S.C. § 262; 21 C.F.R. § 601.2.

information in the application and any supplemental information requested, the center decides whether to approve the drug based on the product's intended use, effectiveness, and the risks and benefits for the intended population. All medical products are associated with some level of risk, and a product is considered safe if its risks are determined to be reasonable given the magnitude of the benefit expected. For decisions on drugs, CDER may approve the product for marketing (in an "approval letter") or it may indicate (in an "approvable letter") that it can approve the drug if the sponsor resolves certain issues. Alternatively, it may issue a "nonapprovable letter" that specifies the issues that make the application ineligible for FDA approval. The review process is similar for biologics; however, CBER issues a "complete response letter" that specifies all outstanding issues that would need to be addressed by the sponsor to be considered for FDA approval.

The review process may consist of more than one review cycle. The first review cycle begins when an NDA or a BLA is initially submitted to FDA, and it ends when FDA has completely reviewed the application and issued some form of an action letter. If the application is approved in the first cycle, the "approval time" is recorded as the length of that cycle. The next cycle of review, if necessary, begins when the application is resubmitted to FDA. If the review process takes two or more cycles to reach approval, the length of the approval time is recorded as the total of the length of the review cycles plus any subsequent time during which a sponsor is addressing the issues raised by FDA.

PDUFA User Fees and Performance Goals

Under PDUFA, companies pay three types of user fees to FDA—application fees, establishment fees, and product fees. In most cases, a company seeking to market a new drug or biologic in the United States must pay an application fee to support the agency's review process.[8] Generally, companies also pay an annual establishment fee for each facility in which their products subject to PDUFA are manufactured and an annual product fee for marketed drugs for which no generic versions are available.

[8]Certain NDAs or BLAs are exempt from user fees. For example, applications for certain drugs used in the treatment of rare diseases are exempt from fees. From fiscal year 1997 through fiscal year 2001, about 22 percent of applicants, on average, paid no application fee.

FDA is expected to use funds received under PDUFA to meet certain performance goals. Under the framework established by PDUFA, FDA works with various stakeholders, including representatives from consumer, patient, and health provider groups and the pharmaceutical and biotechnology industries, to develop performance goals. The Secretary of Health and Human Services (HHS) then transmits these goals in a letter to the Congress.[9] Under PDUFA I, the performance goals applied to length of review time; the performance goals in PDUFA II further shortened the review time and added new performance goals associated with reviewer responsibilities for interacting with the manufacturer, or sponsor, during drug development. For example, PDUFA II required FDA to schedule meetings and respond to various manufacturer requests within specified time frames.

To collect and spend user fees under PDUFA I, each year FDA had to spend from its annual appropriation for salaries and expenses at least as much, adjusted for inflation, on the human drug and biologic review process as it had spent on for this process in fiscal year 1992. Under PDUFA II, each year FDA has to spend at least as much, adjusted for inflation, as it did in fiscal year 1997.

The user fees collected under PDUFA cover only those CDER or CBER activities that are included in the human drug review process. The fees do not fund other CDER or CBER activities and do not fund the programs of the other FDA centers, that is, the Center for Food Safety and Applied Nutrition, Center for Veterinary Medicine, Center for Devices and Radiological Health, and National Center for Toxicological Research. FDA designates the programs of these centers as non-PDUFA programs or other activities.

[9]The legislation refers to these goals identified in a letter to the Congress from the Secretary of HHS. See, for example, P.L. 107-188, Title V, § 502(4).

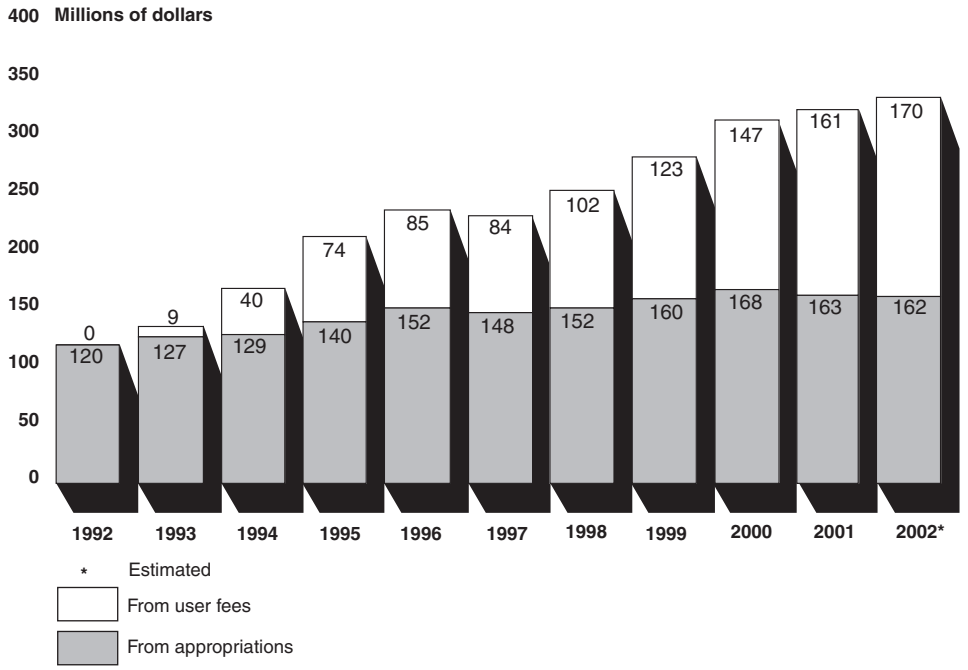
PDUFA Has Increased Funding and Reduced Drug Approval Time, but Biologic Approval Time Has Fluctuated

PDUFA has provided FDA with additional resources that have helped the agency make new drugs available to the U.S. health system more quickly, but biologic approval times have varied. FDA has used PDUFA funds to increase the number of medical and scientific reviewers to assess the applications for new products by about 77 percent. Since 1993, FDA median approval times for standard drugs decreased from about 27 months in 1993 to about 14 months in 2001. However, in recent years, median approval times for standard NMEs have increased. In contrast, median approval times for biologic applications have fluctuated since 1993, ranging from a low of 12 months to a high of about 32 months. In all but 2 years since 1993, approval times for biologics have been longer than for drugs. For example, in 2001, the median approval time for biologics was about 22 months, while median approval times for priority and standard drugs were about 6 months and 14 months, respectively. The fluctuation in BLA approval time is due, in part, to the small number of submissions each year.

User Fees Have Provided Increased Funding for the Review of Drug and Biologic Applications, but Recent Revenues Fell Short of Estimates

Since the implementation of the PDUFA program, user fees have grown steadily and represent an increasing share of FDA's funds for the review of new drug and biologic applications. From fiscal year 1993 through fiscal year 2001, FDA obligated $825 million from user fees for the drug and biologic review processes, in addition to $1.3 billion from its annual appropriation for salaries and expenses (see fig. 1). While user fees funded 7 percent of drug and biologic review obligations in fiscal year 1993, user fees accounted for nearly 50 percent of the total funds obligated for the drug and biologic review processes in fiscal year 2001. In fiscal year 2002, FDA expects to obligate about $170 million in user fees, or 51 percent of the $332 million that FDA expects to spend on its drug and biologic review processes. From fiscal year 1993 to fiscal year 2001, user fees allowed FDA to increase the personnel assigned to review new drug and biologic applications from about 1,300 to about 2,300 full-time equivalents (FTE), an increase of about 77 percent.

Figure 1: Total Obligations for FDA's Drug and Biologic Review Processes, Fiscal Years 1992-2002



Source: FDA.

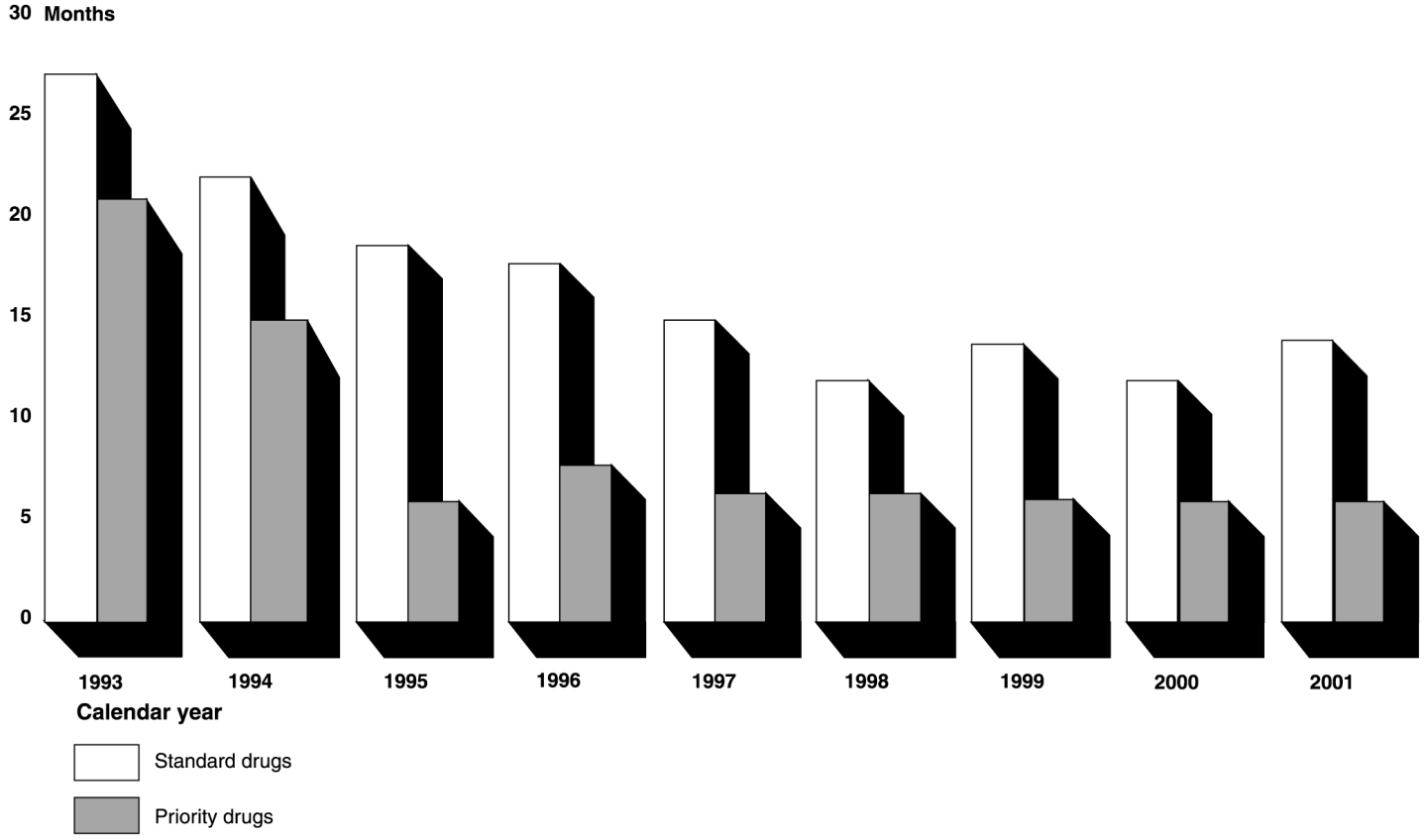
Despite the growth of user fees, user fee revenues under PDUFA II fell short of FDA's estimates, while reviewer workload increased. FDA's estimate of how much the agency would receive from user fees fell short because FDA received fewer submissions than expected. From fiscal year 1998 through fiscal year 2002, FDA collected about $57 million less in user fees that it initially estimated. At the same time, the workload of FDA reviewers increased under PDUFA II. As a result, during the last 2 years of PDUFA II, FDA had to spend unobligated user fees that had been carried over from previous years to maintain its reviewer workforce. Under PDUFA III, FDA will be better able to ensure the stability of user fee revenues.

Median Approval Time for Drugs Has Dropped

Overall, the median approval time for new drugs has dropped since the implementation of PDUFA. From 1993 to 2001, the median approval time for standard new drug applications dropped from about 27 months to

about 14 months (see fig. 2). During the same period, the median approval time for priority new drugs also dropped, from about 21 months to about 6 months. Since 1995, approval times for priority new drugs have been relatively constant.

Figure 2: Median Approval Times for Standard and Priority Drug Applications Based on Calendar Year of Approval, 1993-2001



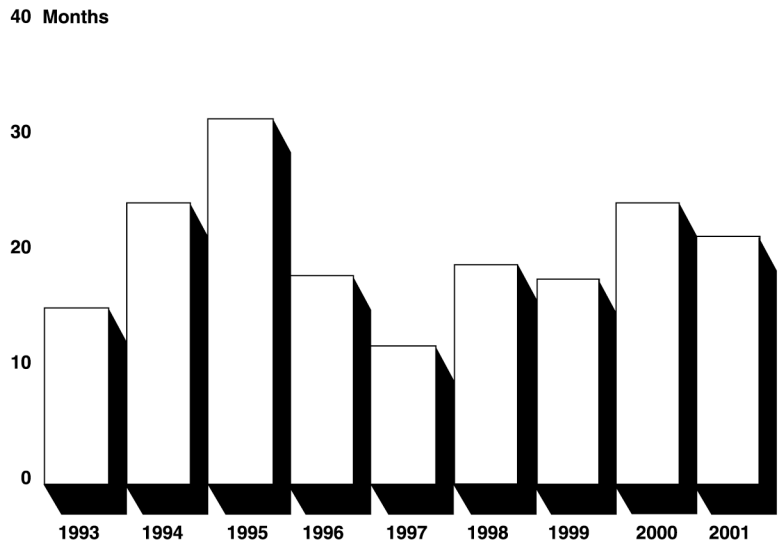
Source: FDA.

While, in general, approval times for new drugs have dropped significantly, the median approval time for standard NMEs, a subset of standard drugs, has increased in recent years. The approval time for standard NMEs reached a low of about 13 months in 1998 before rising to about 20 months in 2000 and 2001. The median approval time for priority NMEs has remained stable at about 6 months since 1997.

Median Approval Time for Biologics Has Fluctuated

The median approval time for a biologic application has varied considerably post-PDUFA, although the small number of biologic applications approved in any given year may affect the variation in approval time. The median approval time increased from about 15 months in 1993 to a high of about 32 months in 1995. After dropping to a low of 12 months in 1997, it rose again and was about 22 months in 2001 (see fig. 3). In all but 2 years since 1993, approval times for biologics have been longer than for drugs.

Figure 3: Median Approval Times for Biologic Applications Based on Calendar Year of Approval, 1993-2001



Source: FDA.

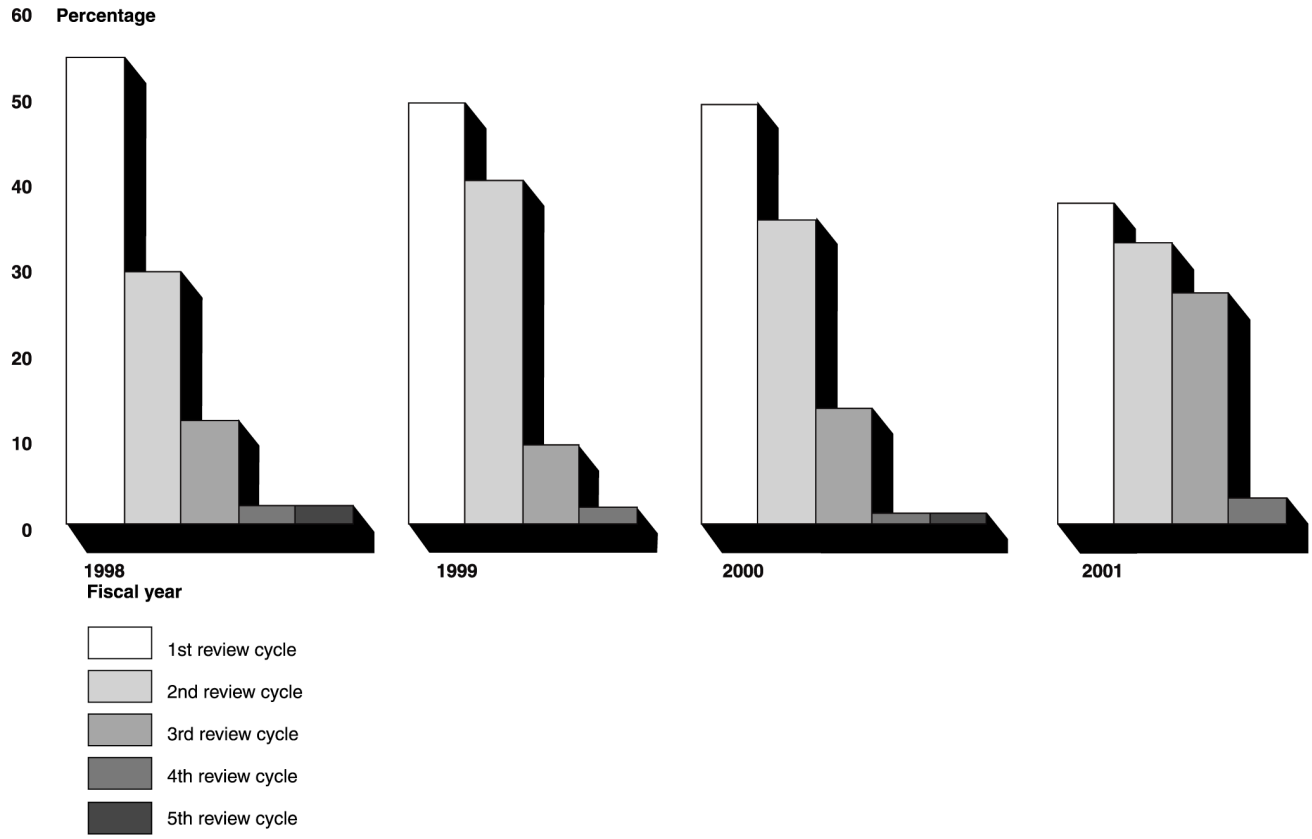
Several Factors Contributed to Recent Increases in FDA Approval Times for NMEs and Biologics

Although there has been an overall decrease in the approval times for standard drug applications since the implementation of PDUFA, FDA approval times for standard NME applications (a subset of standard drugs) and biologic applications have increased recently. According to FDA, approval times for these two types of applications went up in 2000 because many of them had to go through several review cycles before they were approved. Multiple review cycles have occurred for several reasons. For example, after its initial review of an application, FDA may ask the sponsor to provide new information, such as new clinical trials or data analyses, to address deficiencies in the initial application. Once the sponsor provides the requested information, FDA undertakes another

review cycle to examine the information. Also, if FDA completes its assessment late in the review cycle, it can be difficult to resolve issues with the sponsor before the review decision deadline. In these cases, FDA may issue an approvable letter that advises the sponsor that the application will be approved if certain issues are resolved. Issuing an approvable letter enables FDA to meet its performance goals without making a final decision on the application. It also results in the application going through another review cycle.

Both FDA and the pharmaceutical/biotechnology industry have acknowledged that to allow FDA to meet PDUFA review goals, drug and biologic applications are going through more review cycles. While the industry's goal is to obtain approval of an application, FDA can meet the PDUFA goal by completing its review and issuing an action letter. Our analysis of approvals confirms that an increased proportion of applications are going through several review cycles. A smaller percentage of drugs was approved in the first review cycle in 2001 than in previous years (see fig. 4). For example, in 1998, 54 percent of standard new drugs and biologic applications were approved in the first review cycle. In 2001, 37 percent of standard new drugs and biologic applications were approved in the first review cycle. In response to industry's concerns, FDA and the pharmaceutical/biotechnology industry have agreed that the agency will notify an applicant of deficiencies identified within a specified time frame after an application is filed with FDA. While an application may be sufficiently complete for FDA to do a substantive review, the purpose of FDA's communication is to alert a company early to deficiencies in its application that will prevent FDA approval so that it can start addressing them.

Figure 4: Percentage of Standard New Drug and Biologic Applications Approved, by Review Cycle, Fiscal Years 1998-2001



Source: GAO analysis of FDA data.

Additional factors may affect approval times for biologic products. A CBER official stated that the complexity of cutting-edge technology involved in developing and manufacturing biologics, such as gene therapy and bioengineering, may increase approval time. In addition, an FDA official told us that some biotechnology companies have had difficulties demonstrating their ability to consistently manufacture products comparable to those used in their human studies, while others have filed applications with significant clinical and safety issues that had to be resolved. According to a CBER official, the center plans to issue more refuse-to-file letters in such situations at the start of the review cycle to obtain better-quality applications. CBER officials believe that initiating a review of an application that is substantially incomplete, for example, because it omits critical data, or one that raises significant issues is

inherently inefficient and extends review time. A refuse-to-file letter alerts a company to corrective actions that need to be taken so that the FDA review of an application proceeds more promptly and efficiently.

As part of its performance goals established for PDUFA III, FDA agreed to select and hire an outside consultant in fiscal year 2003 to conduct a comprehensive review and analysis of the drug and biologic review process and make recommendations for improvements. User fees will pay for this review and analysis. FDA anticipates delivery of a report of the consultant's findings and recommendations in fiscal year 2005. The agency would then consider these recommendations in planning any changes to enhance its performance.

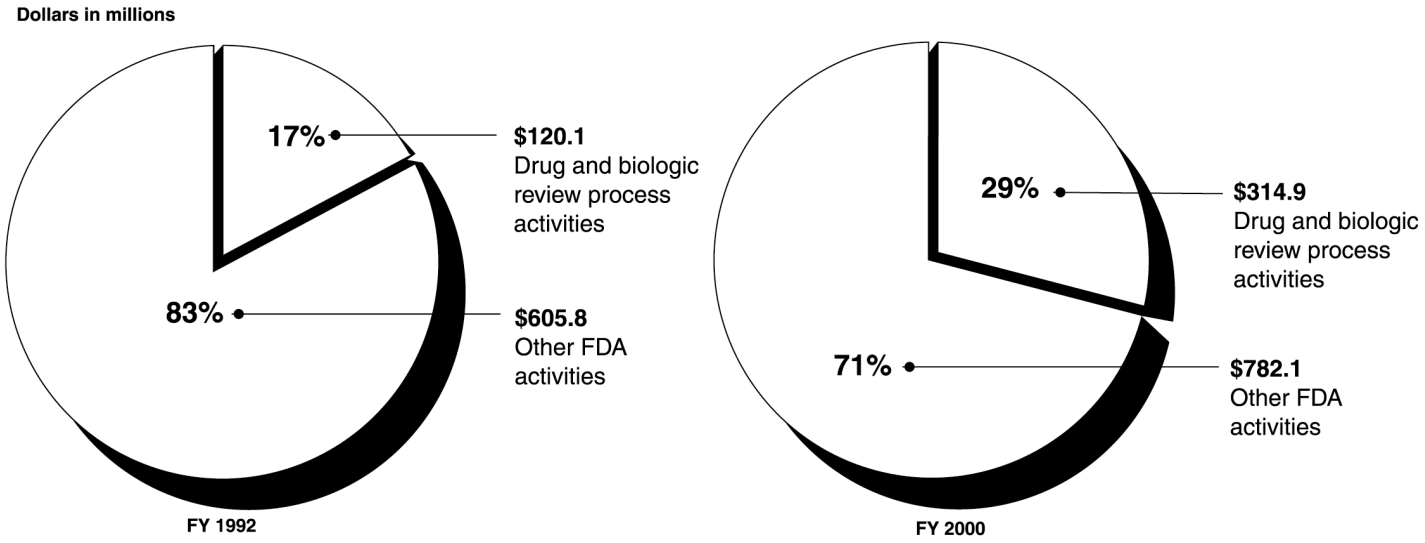
Reduced Share of Funds Available for Other FDA Activities

While PDUFA has increased the funds available for FDA's drug and biologic review activities, funds for FDA's other activities have constituted a smaller portion of FDA's total budget since implementation of PDUFA. According to FDA officials, two factors may have contributed to the reduced share of FDA funds allocated to other activities. First, PDUFA requires that each year FDA spend increasing amounts from its annual appropriation on the drug and biologic review process in order to collect and spend user fee revenues. According to agency officials, FDA had difficulty determining the amount spent until the end of the year. As a result, FDA spent more than was required. Second, FDA officials said that during fiscal years 1994 through 2001, the agency did not receive sufficient increases in its annual appropriation for salaries and expenses to cover annual pay increases for all employees. To ensure that the agency could meet the spending baseline for the drug review program and fund the pay raises, FDA officials reduced available resources for other activities, such as reviewing over-the-counter and generic products and inspecting medical product manufacturing facilities.

Share of Funding and Resources for Other Activities Have Decreased

Since the enactment of PDUFA, the share of FDA funding and the resources available for other activities have decreased. While spending on FDA's other activities rose from about $606 million in fiscal year 1992 to about $782 million in fiscal year 2000, the percentage of FDA funds spent on other activities declined from about 83 percent of FDA's budget in fiscal year 1992 to about 71 percent in fiscal year 2000 (see fig. 5).

Figure 5: Percentage of FDA Funds Obligated for the Drug and Biologic Review Processes and for Other FDA Activities, Fiscal Years 1992 and 2000

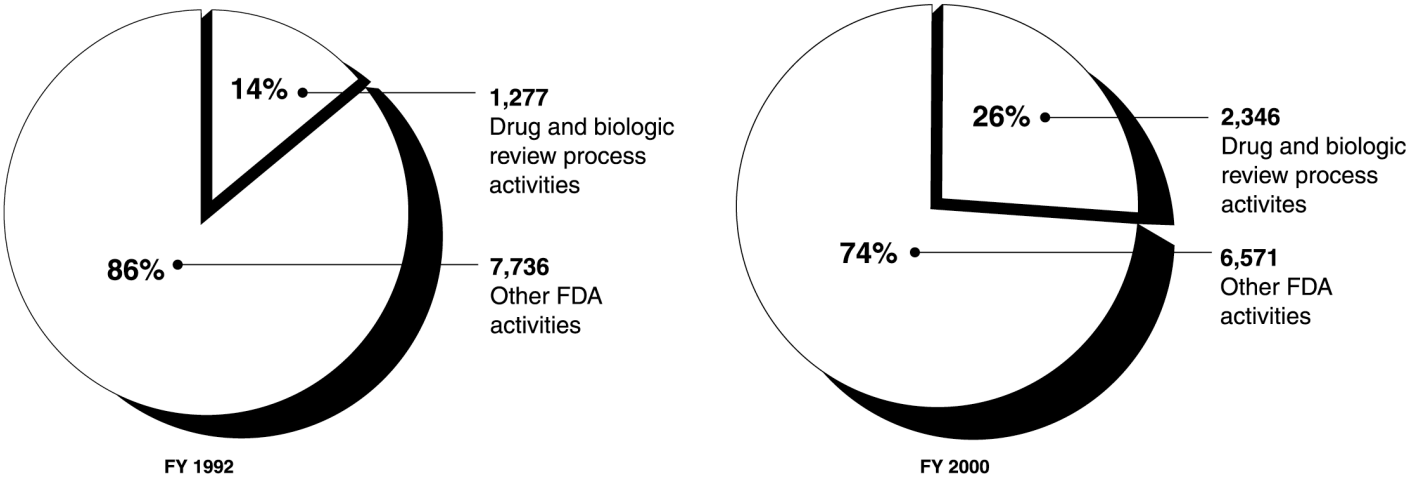


Note: Total FDA obligations were $725,897,020 in 1992 and $1,097,067,544 in 2000 and exclude rental payments to the General Services Administration and building and facilities expenditures.

Source: FDA.

During the same period, FDA resources allocated to other activities declined from 7,736 FTEs in fiscal year 1992 to 6,571 FTEs in fiscal year 2000, or a decline from about 86 percent of FDA's FTE resources in fiscal year 1992 to about 74 percent in fiscal year 2000 (see fig. 6). During the same period, the number of FTEs allocated to drug and biologic review activities rose from 1,277 FTEs in fiscal year 1992 to 2,346 FTEs in fiscal year 2000—an increase from 14 to 26 percent of FDA's total FTEs.

Figure 6: Percentage of FTEs for the Drug and Biologic Review Processes and All Other FDA Activities, Fiscal Years 1992 and 2000



Note: Total FTEs for FDA were 9,013 in 1992 and 8,917 in 2000.

Source: FDA.

Spending for Drug and Biologic Reviews for PDUFA Activities Reduced Funds for Other Activities

According to agency officials, the requirement that FDA must annually increase by an inflation factor the amount it spends on the drug and biologic review processes from its appropriation for salaries and expenses reduces the funds available for other FDA programs. Under PDUFA, if FDA's spending from its appropriation on drug and biologic review activities falls below the statutory minimum, it cannot collect and spend user fees to review drug and biologic applications. FDA would then have to initiate a reduction-in-force because the agency would not have sufficient funds to pay the salaries of the reviewers. FDA officials stated that it is difficult to determine exactly how much the agency has spent from its appropriation until the end of the fiscal year when a final accounting is completed. Therefore, the agency spends more on drug and biologic review activities than the statutory minimum to ensure that it spends enough to continue the user fee program. In 7 of the 9 years since PDUFA was enacted, FDA has exceeded the spending baseline by from 3 to 10 percent (see table 1). In 1996 and 1997, the overspending was higher, 23 and 18 percent, respectively. According to an FDA official, the higher overspending occurred in those years because the agency was particularly focused on meeting the goals established by PDUFA I and spent additional funds to ensure that it met PDUFA's performance goals.

Table 1: FDA Spending Above Amount Required by PDUFA, Fiscal Years 1993-2001

			Difference	
Fiscal year	Minimum spending required by PDUFA	Actual spending from appropriations	Amount	Percentage
1993	$120,057,253	$126,515,577	$6,458,324	5
1994	123,380,438	129,337,138	5,956,700	5
1995	126,958,144	139,830,318	12,872,174	10
1996	124,302,476	152,289,387	27,986,911	23
1997	125,872,166	147,959,689	22,087,523	18
1998	147,959,689	151,836,635	3,876,946	3
1999	150,083,954	159,669,575	9,585,621	6
2000	153,508,177	167,646,122	14,137,945	9
2001	158,213,295	162,691,657	4,478,362	3

Source: FDA.

To the extent that FDA spends more than the minimum amount of its appropriation on drug and biologic review activities under PDUFA, it has less to spend on other activities. As part of PDUFA III, the Congress revised the minimum spending requirement to lessen the potential for the agency to spend more than necessary from its appropriation each year on drug and biologic review activities. Specifically, FDA will be allowed to spend up to 5 percent less than the amount required by law provided that user fee collections in a subsequent year are reduced by the amount in excess of 3 percent that was underspent.[10]

Unfunded Employee Costs Have Reduced FDA's Flexibility to Fund Other Activities

According to FDA officials, the agency reduced staffing levels in other centers to cover the costs of unfunded pay raises. From fiscal years 1994 through 2001, FDA paid about $250 million to cover mandatory federal pay raises for which it did not receive increases in its appropriations. FDA officials told us that this situation reduced the agency's ability to support activities not funded by PDUFA. FDA reduced the staffing levels for non-PDUFA activities each year, leaving the agency fewer resources to perform its other responsibilities. For example, in its budget justification for fiscal year 2002, FDA reported that inspection of medical device

[10]Under PDUFA III, if FDA underspends by 3 percent or less, there is no penalty. However, if FDA underspends by more than 3 percent but not more than 5 percent, the agency will be required to reduce user fee collections in a subsequent year by the amount in excess of 3 percent that was underspent.

manufacturers has decreased and the agency does not routinely inspect the manufacturers of lower-risk products. Although total FDA staffing in fiscal year 2001 was about the same as in fiscal year 1992, about 1,000 more FTEs were allotted to drug and biologic review activities in fiscal year 2001 and about 1,000 fewer FTEs were allotted to other FDA programs that ensure food safety, approve new medical devices such as heart valves and pacemakers, and monitor devices once on the market.

Although FDA received a number of funding increases during this period, FDA officials told us that in general those funds could not be used for across-the-board pay increases because almost all funding increases received since 1992 were earmarked for designated programs. FDA officials said that some of the funding increases were for programs related to tobacco, food safety, Internet drug sales, orphan product grants, and dietary supplements. According to FDA, $45.2 million was available to cover pay increases for the agency's employees in its fiscal year 2002 appropriation. In addition, the President's budget for fiscal year 2003 includes $28.6 million for pay increases.

PDUFA Has Contributed to Increased Workload and Attrition and Decreased Training for FDA Reviewers

FDA officials told us that the performance goals added by PDUFA II, combined with PDUFA II's shortened review timelines, have contributed to a heavy workload for FDA's reviewers, which has resulted in high turnover and reviewers forgoing training and professional development activities. Our review of FDA data and a recent report by KPMG Consulting found that FDA's workload under PDUFA has increased.[11] Moreover, our analysis of FDA and OPM data found that FDA's attrition rates for many of the occupations that are involved in its drug review process are higher than those for other federal public health agencies and the federal government as a whole. In addition, KPMG's report found that FDA reviewers were not receiving the amount of training FDA considers necessary. According to FDA officials, the agency needs significant and sustained increases in funding to hire, train, and retain its review staff in order to continue meeting PDUFA performance goals, provide quality scientific and regulatory advice to the industry, and avoid further deterioration in retention rates.

[11]KPMG Consulting, *Reanalysis of 1993 Standard Costs for the Process for the Review of Human Drug Applications As Required Under the Prescription Drug User Fee Act* (McLean, Va.: March 2002).

PDUFA II Resulted in Increased Reviewer Workload

PDUFA II affected reviewer workload by shortening review times and adding new performance goals to reduce overall drug development time—the time needed to take a drug from clinical testing to submission of a new drug or biologic application. As part of the performance goals established for PDUFA II and transmitted to the Congress,[12] FDA agreed, for example, to complete review of 90 percent of standard new drug applications and efficacy supplements filed in fiscal year 2002 within 10 months—a decrease from the 12-month goal set in PDUFA I for fiscal year 1997. In addition, FDA agreed to complete review of 90 percent of manufacturing supplements within 4 months—a decrease from the 6-month goal in PDUFA I.[13] PDUFA II also established a new set of performance goals intended to improve FDA's responsiveness to and communication with drug sponsors during the early years of drug development. Specifically, FDA agreed to

- review a sponsor's request for a formal meeting and provide written notification to the sponsor of its decision within 14 days;
- schedule major meetings at critical milestones during drug development within 60 days of request, and all other meetings within 75 days of request;
- prepare meeting minutes within 30 calendar days of a meeting;
- respond to a sponsor's request for evaluation of special protocol designs within 45 days;
- respond to a sponsor's complete response to a clinical hold within 30 days; and
- respond to a sponsor's appeal of a decision within 30 days.

In general, the number of FDA review activities increased in fiscal years 1999 through 2001 because of the performance goals added under PDUFA II (see table 2). Specifically, the increases occurred in the activities related to the requirement that FDA work with drug sponsors in the early phases of drug development. Meeting requests, meetings, and meeting minutes constituted a growing portion of FDA review activities.

[12]P.L. 105-115, Title 1, § 101(4) refers to the PDUFA II performance goals transmitted in a letter to the Congress from the Secretary of HHS.

[13]FDA agreed to review in 4 months only those manufacturing supplements that require agency approval before manufacturers can make changes.

Table 2: Number of Submission and Review Activities Under PDUFA II, by Fiscal Year

	Fiscal year			
Activity	**1998**	**1999**	**2000**	**2001**
Ongoing submission activities				
Review of NDA/BLA	121	127	134	101
Review of efficacy supplements	136	145	187	168
Review of manufacturing supplements	1,834	1,936	2,025	2,069
Review of investigational new drug applications	746	638	738	699
New review activities added under PDUFA II in FY 1999				
Respond to meeting requests from industry	N/A	1,544	1,183	1,471
Schedule meetings	N/A	1,468	1,121	1,361
Prepare meeting minutes	N/A	1,335	1,009	1,222
Respond to clinical holds	42	124	133	159
Respond to protocol designs	N/A	69	128	121
Respond to sponsors' appeals of decisions in major dispute resolution	N/A	7	13	11

Note: N/A means not available. Responses to clinical holds was the only new review activity that FDA tracked beginning in fiscal year 1998. FDA did not measure the number of the other submissions before the enactment of PDUFA II.

Source: FDA.

According to FDA reviewers, the typical meeting between FDA and a sponsor during clinical testing involves 17 reviewers from six disciplines that are typically involved in reviews of new drug and biologic applications—medical officer, chemist, microbiologist, clinical pharmacologist, statistician, and pharmacologist/toxicologist. FDA reviewers estimate that the time requirements for a comprehensive meeting involving all FDA review disciplines assigned to an application can range from about 125 to 545 hours per meeting.[14] For example, reviewers estimated that the total FDA staff time spent reviewing the briefing document submitted by the sponsor as well as reviewing other pertinent documents and consulting with other review team members and consultants ranges from 50 to 290 hours. Reviewers estimated that from about 25 to 90 FDA staff hours are spent interacting with the sponsor in final preparation for the meeting, including requesting additional information from the sponsor and reviewing information submitted,

[14]FDA officials told us a range is the best way to capture the burden of meetings because each meeting request and new drug or biologic application is different in the complexity of the issues and the adequacy of the information submitted by the sponsor.

developing the meeting agenda, preparing presentations, and attending the actual meeting with the sponsor, which generally lasts 90 minutes to 2 hours.

FDA's workload was further affected by an increase in the number of applications that did not require payment of user fees, due to PDUFA II's new exemptions and waiver provisions. Under PDUFA II, FDA could exempt or waive fees for (1) drug sponsors that were small businesses submitting their first applications, (2) drug sponsors submitting supplements for drugs used to treat pediatric illnesses, and (3) drug sponsors submitting applications or supplements for drugs used to treat rare diseases (called orphan drugs). FDA officials told us that the percentage of applications where user fees were exempted or waived was significant, ranging from a low of 19 percent in fiscal year 1999 to a high of 32 percent in fiscal year 2001.

The KPMG report on FDA's drug review costs found that the new performance goals established for PDUFA II have also had a significant impact on reviewer workload. According to the report, the majority of reviewers interviewed reported that the new performance goals for meetings with drug sponsors were burdensome. They said that competing priorities made it difficult to complete all tasks, such as accommodating meeting requests, participating in advisory committee meetings, and answering sponsor questions.

FDA's Reviewer Attrition Level Is Higher than That of Comparable Occupations in Other Federal Agencies

Our analysis of FDA's attrition rates for drug reviewers during the 3-year period following the enactment of PDUFA II found that they were higher than the rates for comparable occupations at other public health agencies and in the federal government as a whole. FDA officials told us that the agency continues to experience high turnover for reviewers because of the high demand for regulatory review personnel in the pharmaceutical industry and the higher salaries that experienced FDA reviewers can obtain in the private sector. Attrition of FDA reviewers has been an ongoing concern for the pharmaceutical and biotechnology industries as well. An independent survey of pharmaceutical and biotechnology

companies found a high level of concern about FDA's turnover in review staff and an increase in concern over a 4-year period.[15]

We compared FDA's attrition rate for the six medical and scientific disciplines that constitute the majority of the agency's drug review staff with the attrition rates for these disciplines at the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) (see table 3). Like FDA, CDC and NIH are public health agencies that employ a highly educated, highly skilled workforce. As the table shows, with the exception of chemists, FDA's attrition rates for employees in its drug review process are higher than the comparable attrition rates for CDC, NIH, and similar disciplines governmentwide.

Table 3: Average Attrition Rates for Selected Occupations in FDA, CDC, NIH, and Governmentwide, Fiscal Years 1998-2000

		Average attrition rate (percentage) for 1998-2000			
Occupation	**GS**	**FDA**	**CDC**	**NIH**	**Governmentwide**
Biologist	401	9.5	3.9	6.8	5.2
Microbiologist	403	9.3	4.3	4.8	4.6
Pharmacologist	405	9.6	0.0	3.7	7.4
Medical officer	602	10.5	5.5	4.7	9.0
Chemist	1320	5.8	4.2	5.4	6.1
Mathematical statistician	1529	14.1	3.9	3.7	7.3

Sources: FDA and OPM.

FDA officials reported that to retain experienced staff with certain skills, they have increased the pay for approximately 250 CDER and CBER reviewers. Specifically, FDA conducted studies of staff turnover and found that toxicologists, pharmacologists, pharmacokinetists, and mathematical statisticians were leaving FDA to work in private industry and academia for higher salaries. Under OPM regulations, FDA is authorized to pay retention allowance of up to 10 percent of an employee's basic pay to a group or category of employees in such circumstances. Employees with at least 2 years of drug review experience in these 4 occupations were

[15]PricewaterhouseCoopers and University of California at San Diego's Technology and Entrepreneurship Program (UCSD CONNECT), *Improving America's Health III: A Survey of the Working Relationship Between the Life Sciences Industry and the FDA, 2000 Update* (San Diego, Calif.: December 2000). www.pwcglobaltech.com (downloaded on April 23, 2002).

eligible for retention allowances. In addition, 5 medical officers and 1 microbiologist were among review staff that received retention allowances. FDA is also considering offering retention allowances to all of its medical officers.

FDA Says Reviewers Forgo Training and Professional Development to Ensure PDUFA Goals Are Met

We found that FDA reviewers, particularly those in CBER, did not participate in training and professional development activities to the extent recommended by the agency in fiscal years 2000 and 2001. FDA officials told us that reviewers are forgoing training and professional development activities to ensure that the agency meets PDUFA goals. FDA defines training and professional development activities as time spent

- attending related training and conferences, whether as a presenter or an attendee;
- learning the review process for drug applications and labeling under a mentor;
- preparing educational material, publications, and manuscripts or classroom or seminar-type instruction; and
- mentoring a new reviewer.

FDA reviewers are encouraged to spend about 10 percent of their time in training, professional development, and mentoring activities. According to FDA, other science-based agencies, such as NIH, expect scientists to spend about 20 percent of their time on training and professional development. Using KPMG's estimate that each full-time FDA reviewer worked 200 days per year, FDA's 10 percent recommended level of training means that each reviewer would be encouraged to spend 20 days per year in training and professional development activities. Our analysis of FDA data found that reviewers in CDER spent, on average, about 19 days in training and professional development activities in fiscal years 2000 and 2001. However, we found that reviewers in CBER spent, on average, about 12 days in training and professional development activities in fiscal years 2000 and 2001.

FDA spending for PDUFA-related training and other professional development activities has fluctuated greatly over the past 3 years. Expenditures for PDUFA-related training and other professional development activities in CDER rose from $285,000 in fiscal year 1998 to $796,000 in fiscal year 1999, then dropped to $564,000 in fiscal year 2000. CBER's expenditures increased from $198,882 in fiscal year 1998 to $206,655 in fiscal year 1999, then dropped to $147,914 in fiscal year 2000, a 26 percent decline from the 1998 level.

FDA reviewers, as well as representatives from pharmaceutical and biotechnology companies, are concerned about reviewers' lack of time for training and professional development. The KPMG report found that reviewers perceived insufficient training to be a major problem. The reviewers interviewed reported that while they wanted to ensure that they were at the cutting edge of medical technology and were able to effectively use workplace tools such as information systems, they believed they had insufficient time to complete training. In addition, an independent survey of pharmaceutical and biotechnology companies found a high level of concern in the industry related to a perceived lack of technical expertise among FDA reviewers. According to the survey, 27 percent of the respondents indicated that reviewer lack of expertise impeded the approval process. That figure increased from a 19 percent rate in the 1997 survey and 17 percent in 1995.[16]

Rate of Safety-Related Drug Withdrawals Has Increased Recently

Some consumer and patient groups have raised concerns that drug withdrawal rates have increased under PDUFA. Our analysis of FDA data found that the percentage of recently approved drugs that have been withdrawn from the market has risen, but that the size of the increase in drug withdrawal rates differs depending on the period examined. Moreover, several factors may affect drug withdrawals. Some drugs were removed from the market because doctors and patients did not use them correctly, while others produced rare side effects that were not detected in clinical trials. The availability of new, safer treatments also led to some withdrawals. For drugs approved under PDUFA III, FDA may use user fees to support its drug safety efforts.

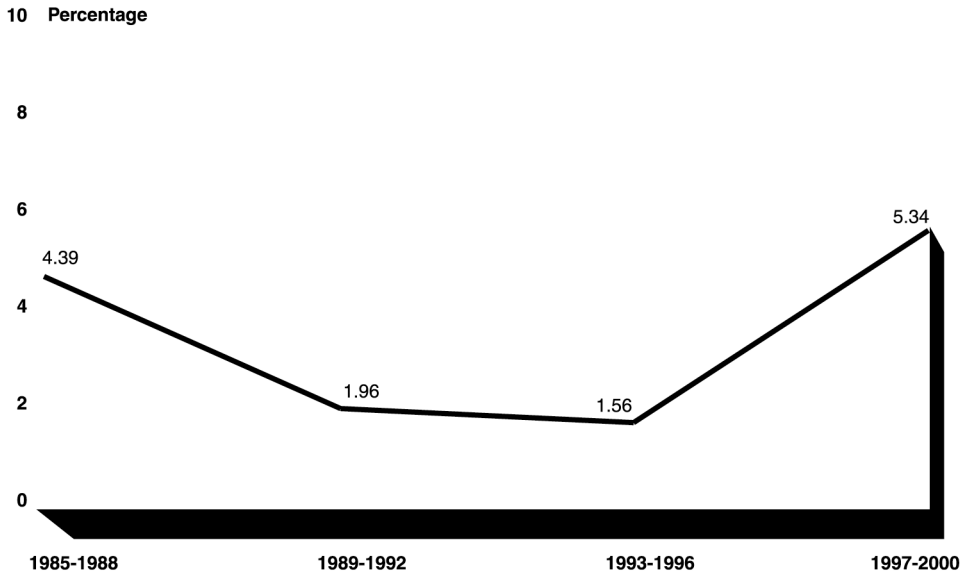
Size of the Increase in Drug Withdrawal Rates Differs Depending on the Period Examined

Our analysis of FDA data found that a higher percentage of drugs has been withdrawn from the market for safety-related reasons since PDUFA's enactment than prior to the law's enactment. Some consumer and patient groups have expressed concern that PDUFA's emphasis on faster review times has increased the rate of withdrawals and compromised drug safety by placing FDA reviewers under pressure to approve drugs rapidly to meet performance goals. We identified each drug that was withdrawn from the market from 1985 through 2000, and grouped the withdrawals based on the year in which the drug was approved. We then calculated the drug

[16]UCSD CONNECT, *Improving America's Health III: A Survey of the Working Relationship Between the Life Sciences Industry and the FDA, 2000 Update.*

withdrawal rate—the number of withdrawn drugs as a percentage of those approved each year. We calculated drug withdrawal rates in 4-year intervals over 16 years. As shown in figure 7, the withdrawal rate declined from 1.96 percent for 1989 through 1992 (the 4 years preceding PDUFA) to 1.56 percent for 1993 through 1996 (under PDUFA I), then rose to 5.34 percent for 1997 through 2000 (under PDUFA II). However, the small number of withdrawals in any given year may affect the variation in the withdrawal rate.

Figure 7: Rate of Safety-Related Drug Withdrawals by 4-Year Intervals, Based on Calendar Year of Approval, 1985-2000

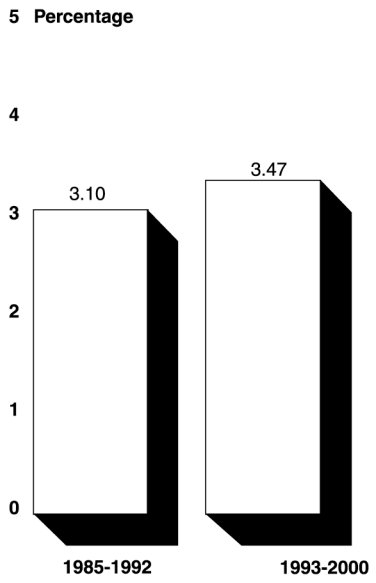


Note: These drugs are classified as NMEs.

Source: GAO analysis of FDA data.

We also calculated the withdrawal rate with reference to whether the drug was approved in the 8-year period before or the 8-year period after PDUFA was enacted. Grouping the withdrawals in these two periods showed that the withdrawal rate increased slightly after PDUFA (see fig. 8). During the period 1985 through 1992 (pre-PDUFA), FDA approved 193 NMEs. Six of these, or 3.10 percent, were withdrawn for safety-related reasons. During the period 1993 through 2000 (post-PDUFA), FDA approved 259 NMEs, and 9 of these, or 3.47 percent, were withdrawn for safety-related reasons.

Figure 8: Rate of Safety-Related Drug Withdrawals Pre- and Post-PDUFA, Based on Calendar Year of Approval, 1985-2000



Note: These drugs are classified as NMEs.

Source: GAO analysis of FDA data.

Drug Withdrawals May Be Affected by Several Factors

Several factors may affect drug withdrawals. According to FDA officials, premarketing clinical trials in a few thousands patients (typically with relatively uncomplicated health conditions) do not detect all of a drug's adverse effects, especially relatively rare ones. In addition, they stated that the rise in the number of newly approved drugs entering the market and the higher consumption of medicines by the population increase the probability of misprescribing, adverse effects, and subsequent drug withdrawals. According to FDA officials, safety problems not detected in clinical trials are more likely to be found first among U.S. patients because they are increasingly first to have access to new drugs. The United States

was the first market for 49 percent of new drugs approved in the United States from 1996 through 1998, according to a study.[17]

An examination of drug withdrawals, by itself, may not provide a complete picture of drug safety. First, a drug withdrawal does not reflect a judgment concerning the absolute safety of a drug but reflects a judgment about the risks and rewards of a drug in the context of alternative treatments. For instance, despite the documented deaths from liver failure among patients taking Rezulin, the drug was not withdrawn from the market until FDA approved new, safer medications with similar benefits. In contrast, Raxar was withdrawn from the market on the basis of relatively few adverse event reports because alternative treatments were readily available. Second, drug withdrawals may occur because health professionals and patients use the drugs incorrectly, not because the drugs are inherently dangerous when used as approved. For example, the health risks associated with Seldane occurred when the drug was taken in combination with medications that were contraindicated on Seldane's label. Third, the off-label use of drugs also can be problematic because such use may not have been shown to be safe and effective. For example, while Pondimin (fenfluramine) was approved for short-term use as an appetite suppressant, it was increasingly prescribed and used in combination with the appetite suppressant phentermine as a part of a long-term weight loss and management program. The off-label use of this combination, known as "fen-phen," posed serious health risks.[18] (See app. I for a list of drugs withdrawn from the U.S. market for safety-related reasons from 1992 through 2001.)

PDUFA III User Fees Will Be Used to Support Additional FDA Drug Safety Efforts

PDUFA III authorizes FDA to use user fees for additional drug safety activities that could not be funded by PDUFA I and II user fees. FDA informed the Congress in its performance goal letter for PDUFA III that it will develop guidance documents to assist the industry in addressing good risk assessment, risk management, and postmarketing surveillance practices. As part of joint recommendations to the Congress for the reauthorization of PDUFA, PhRMA and BIO agreed with FDA that the agency should use user fees to fund a new risk management system for

[17]K.I. Kaitin and E.M. Healy, "The New Drug Approvals Of 1996, 1997, and 1998: Drug Development Trends In The User Fee Era," *Drug Information Journal*, *vol.* 34, no. 1 (2000), pp. 1-14.

[18]The use of phentermine alone has not been associated with valvular heart disease.

newly approved drugs. Under the voluntary program, drug sponsors may develop, and FDA will review, risk management plans for products while the agency reviews the sponsor's NDA or BLA. By adding FDA's postmarket safety team to the drug review process before a new drug or biologic is approved, FDA officials believe that they will obtain better information on the risks associated with the product much earlier in the process and the sponsor will gain helpful feedback on how best to monitor, assess, and control the product's risks.

Funding from user fees will be used to implement risk management plans for the first 2 years after a product is approved. For products that require risk management beyond standard labeling, FDA may use user fees for postmarket surveillance activities for 3 years. FDA officials believe that more rigorous safety monitoring of newly approved drugs during the first few years after they are on the market could help to detect unanticipated adverse effects earlier. Historically, the vast majority of adverse effects have been identified in the first 2 to 3 years after a new drug is marketed. FDA anticipates that user fees for risk management will total approximately $71 million over 5 years, and will permit the agency to add 100 new employees to monitor drug safety and track adverse effects from drugs already on the market (see table 4).

Table 4: FTEs and Dollar Allocations for Risk Management under PDUFA III

Fiscal year	Proposed FTE allocation	Allocation amount (dollars in millions)
2003	19	$8.3
2004	16	11.1
2005	24	15.1
2006	32	17.6
2007	9	18.8
Total	**100**	**$70.9**

Source: FDA.

Conclusions

The implementation of PDUFA has been successful in bringing new drugs and biologics to the U.S. market more rapidly than before. However, maintaining adequate funding for approving new drugs and biologics has had the unintended effect of reducing the share of funding and staffing for other activities. Fewer resources for non-PDUFA programs may affect FDA's ability to ensure that the other products the agency regulates, such as food and medical devices, comply with FDA safety standards. In

addition, PDUFA has increased reviewer workloads and may be a factor in relatively high attrition rates among FDA's review staff.

Rapid FDA approval of new drugs means that the United States has become the first nation to approve many new medicines. Because drugs and biologics are not risk-free, adverse events are to be expected once the products are in the marketplace. As more new drugs and biologics are brought to market, increased attention to postmarket risk management will be even more important. The recent increase in the rate of drug withdrawals also suggests the need for FDA to strengthen its postmarket surveillance activities. Under PDUFA III, FDA will now be able to use user fees for additional drug safety activities, something that was not permitted under PDUFA I and II. By having more resources to review risk management plans developed by drug sponsors and conduct postmarket surveillance, FDA will be able to obtain better information on the risks associated with newly marketed drugs more quickly.

Agency Comments and Our Evaluation

We provided FDA with a draft of this report for comment and FDA provided technical comments. In their technical comments, FDA disagreed with our analyses and discussion related to drug withdrawal rates. Specifically, FDA officials said that our analysis of drug withdrawal data comparing the 8-year period pre-PDUFA with the first 8 years after PDUFA does not show any real increase, and that our analysis using the 4-year groupings was significantly affected by the small number of withdrawals during each period. While we agree that the small number of withdrawals in any given year may affect the variation in the withdrawal rate, we believe our analyses are appropriate and both the 8-year and 4-year analyses show an increase in withdrawal rates since PDUFA's implementation. We incorporated additional technical comments where appropriate. (FDA's comments are included in app. II).

As agreed with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 7 days after its issue date. At that time, we will send copies to the Secretary of HHS, the Deputy Commissioner of FDA, the Director of the Office of Management and Budget, appropriate congressional committees, and other interested parties. We will also make copies available to others on request. In addition, the report will be available at no charge on the GAO Web site at http://www.gao.gov.

Major contributors to this report were John Hansen, Gloria Taylor, Claude Hayeck, and Roseanne Price. If you or your staff have any questions about this report or would like additional information, please call me at (202) 512-7119 or John Hansen at (202) 512-7105.

Sincerely yours,

Janet Heinrich
Director, Health Care—Public Health Issues

Appendix I: Drugs Withdrawn for Safety-Related Reasons from U.S. Market, 1992 Through 2001

Year withdrawn	Drug name	Year approved	Total approval time (months)	Health risks that led to withdrawal
1992	Omniflox (temafloxacin hydrochloride)	1992	26.0	Hypoglycemia, Hemolytic anemia, and kidney failure
1993	Manoplax (flosequinan)	1992	27.0	Increased mortality
1997	Pondimin (fenfluramine hydrochloride)	1973	75.5	Valvular heart disease
1997	Redux[a] (dexfenfluramine hydrochloride)	1996	35.2	Valvular heart disease
1998	Seldane (terfenadine)	1985	26.2	Fatal arrhythmias
1998	Posicor (mibefradil dihydrochloride)	1997	15.3	Fatal arrhythmias
1998	Duract (bromfenac sodium)	1997	27.7	Liver toxicity
1999	Hismanal (astemizole)	1988	46.1	Fatal arrhythmias
1999	Raxar (grepafloxacin hydrochloride)	1997	11.9	Torsade de Pointes arrhythmias
2000	Rezulin (troglitazone)	1997	6.0	Liver toxicity
2000	Propulsid (cisapride)	1993	23.0	Fatal arrhythmias
2000	Lotronex[b] (alosetron hydrochloride)	2000	7.4	Ischemic colitis and severe constipation leading to surgery
2001	Raplon (rapacuronium bromide)	1999	13.8	Bronchospasm
2001	Baycol (cerivastatin sodium)	1997	12.0	Rhabdomyolysis (severe damage to skeletal muscle)

Note: These drugs are classified as NMEs.

[a]While Redux is not an NME, it is included since the combination of Pondimin and Redux, known as "fen-phen" was an off-label use, which resulted in both drugs being withdrawn from the market.

[b]In June 2002, Lotronex was approved for use in a limited population.

Source: FDA.

Appendix II: Comments from the Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

August 30, 2002

Ms. Janet Heinrich
Director, Health Care—Public Health Issues
United States General Accounting Office
441 G Street, NW
Washington, DC 20548

Dear Ms. Heinrich:

Thank you for the opportunity to review GAO's draft report, Food and Drug Administration: Effect of User Fees on Approval Times, Withdrawals, Workload and Funding for Non-User Fee Activities (GAO-02-958). The Agency provided technical comments directly to your staff.

We appreciate your staff's attention to this important topic and the opportunity to work with them in developing this report. The Agency also recognizes your efforts in GAO's May 2002 briefing of the U.S. Senate Committee on Health, Education, Labor, and Pensions, and any part this may have had in passing the Prescription Drug User Fee Amendments of 2002.

Sincerely,

Lester M. Crawford, D.V.M., Ph.D.
Deputy Commissioner

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