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GAO

Report to Congressional Requesters

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FDA DRUG APPROVAL

Review Time Has Decreased in Recent Years

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Program Evaluation and
Methodology Division

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The Honorable Nancy Landon Kassebaum
Chairman
The Honorable Edward M. Kennedy
Ranking Minority Member
Committee on Labor and Human Resources
United States Senate

New drugs marketed in the United States must be approved first by the Food and Drug Administration (FDA).[1] Approval comes after FDA has determined from data submitted by a drug's sponsor that the drug is safe and effective for use as indicated on its label and that the manufacturer can ensure its quality. Various parties calling for the legislative reform of FDA in recent months are concerned with the length of the approval process. Advocates of reform argue that shortening the time it takes to get new drugs approved will contribute both to public health, by making effective therapies available sooner to people who need them, and to the economic health of the pharmaceutical industry, by allowing drug manufacturers to sell their products sooner. Opposed to major reform, FDA claims that in recent years review time has been reduced considerably.

Purpose

Time—specifically the period that begins with the submission to FDA of a new drug application (NDA) and that ends when a final decision is made on that application (the period known as the NDA review phase of drug development)—is the focus of this report. At your request, we have assembled data on all new drug applications submitted to FDA in 1987-94 to answer three questions:

- Has the timeliness of the review and approval process for new drugs changed in recent years?
- What factors distinguish NDAs that are approved relatively quickly from those that take longer to be approved?
- What distinguishes NDAs that are approved from those that are not?

Additionally, as you asked, we obtained the most recently available data on how long it takes for drugs to be approved in the United Kingdom and compared them with approval times in the United States.

[1]See 21 U.S.C. 355 (1988).

Because GAO has access to all applications, both those that have been approved and those that have not, our report is the first to present comprehensive data on review time for all NDAs submitted to FDA.[2]

Background

The process of bringing a drug to market is lengthy and complex and begins with laboratory investigations of the drug's potential. For drugs that seem to hold promise, preclinical animal studies are typically conducted to see how a drug affects living systems. If the animal studies are successful, the sponsoring pharmaceutical firm designs and initiates clinical studies in which the drug is given to humans. At this point, FDA becomes directly involved for the first time.

Before any new drug can be tested on humans, the drug's sponsor must submit an investigational new drug application to FDA that summarizes the preclinical work, lays out a plan for how the drug will be tested on humans, and provides assurances that appropriate measures will be taken to protect them. Unless FDA decides that the proposed study is unsafe, clinical testing may begin 31 days after this application is submitted to FDA. While clinical trials progress through several phases aimed at establishing safety and efficacy, the manufacturer develops the processes necessary to produce large quantities of the drug that meet the quality standards for commercial marketing.

When all this has been done, the pharmaceutical firm submits an NDA that includes the information FDA needs to determine whether the drug is safe and effective for its intended use and whether the manufacturing process can ensure its quality. The first decision FDA must make is whether to accept the NDA or to refuse to file it because it does not meet minimum requirements. Once FDA has accepted an NDA, it decides whether to approve the drug on the basis of the information in the application and any supplemental information FDA has requested. FDA can approve the drug 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, FDA may withhold approval (through a "nonapprovable letter" that specifies the reasons). Throughout the process, the sponsor remains an active participant by responding to FDA's inquiries and concerns. The sponsor has the option, moreover, of withdrawing the application at any time.

[2]Much of the information in an NDA (and even its existence) remains proprietary until FDA approves it. This means that information on NDAs that are not approved has not been publicly available, so that previous studies of review and approval times have been unable to include it.

Method

For each NDA submitted between 1987 and 1994, we obtained from FDA information on the dates of its significant events between initial submission and final decision as well as the last reported status of the application as of May 1995. To ensure that the data were valid, we independently checked them against values in published reports and other sources. (The variables that we used in our analysis and the procedures that we used to validate the data can be found in appendix I.)

We computed time by measuring the interval between all significant events. Results using other ways to calculate review time are compared to ours in appendix II. We used regression analysis to determine the factors that were significantly related to time and to determine which factors were significantly related to approval. (The results of the regression analyses on time are in appendix IV, on approval in appendix V.[3])

Some of our analyses include all the NDAs, while others focus on specific subgroups. Most notably, we restricted analyses of overall time to NDAs that had been submitted by the end of 1992 to avoid the bias introduced by including applications that have had an insufficient time to "mature." (Appendix VI describes the implications of this decision for our results.) Because our analyses of final decisions concentrate on NDAs submitted through the end of 1992, the data we present do not address the consequences of the full implementation of the Prescription Drug User Fee Act of 1992.[4] Our findings pertain only to FDA's Center for Drug Evaluation and Research and do not reflect the activities of the agency's five other centers.[5]

We focused only on the NDA review phase—the final critical step of bringing a drug to market. We did not address the lengthier process of initial exploration and clinical testing, which together with the NDA phase average more than a decade, nor did we study the phase that follows a drug's approval, during which additional studies can be conducted and

[3]In appendix III, we discuss intermediate outcomes from FDA's review process.

[4]The Congress passed the act (Public Law 102-571) in October 1992 to provide FDA with additional resources to expedite drug review and approval. Because it takes time to hire and train reviewers and for fees to accrue, the effects of full implementation may not be evident for several years. The act is due for reauthorization after 1997, by which time FDA has agreed to meet the act's goals for improved performance.

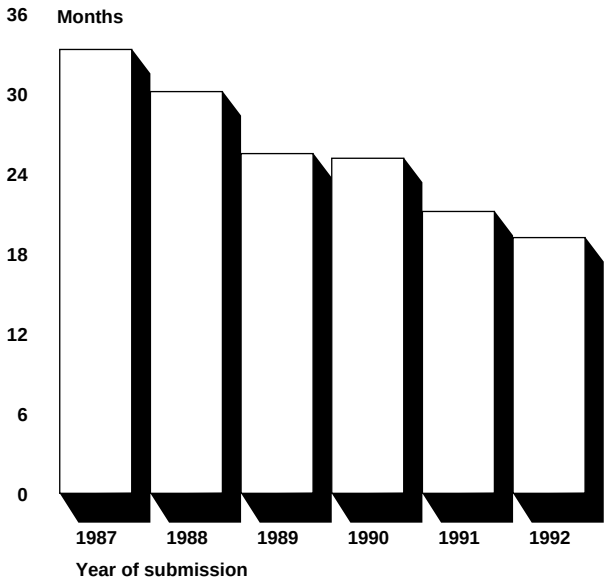
[5]The other centers are the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Center for Food Safety and Applied Nutrition, the Center for Veterinary Medicine, and the National Center for Toxicological Research. Even within the Center for Drug Evaluation and Research, our findings pertain only to the review and approval process for NDAs and not to other functions such as the investigational new drug phase or the regulation of generic drugs.

attention paid to potential adverse events associated with its widespread use in the general population.

Results in Brief

We found a considerable reduction in approval time for NDAs submitted between 1987 and 1992. It took an average of 33 months for NDAs submitted in 1987 to be approved but only 19 months on average to approve NDAs submitted in 1992. Further, the reduction in time was observed for all NDAs and not just for those that had been approved. As figure 1 shows, the overall decrease in approval times was achieved through gradual reductions in time for applications submitted in each successive year.

Figure 1: Months Between Submission and Approval for NDAs Submitted 1987-92[a]



[a]Number of approved NDAs: 1987, 80; 1988, 75; 1989, 65; 1990, 53; 1991, 64; 1992, 53.

The priority FDA assigns to an NDA and the experience of its sponsor are the two factors that significantly affect the likelihood that the NDA will be decided on quickly. FDA assigns priority status to applications for drugs that are expected to provide therapeutic benefit to consumers beyond that of drugs already marketed. These NDAs take an average of 10 months less to be approved than do standard applications (those for which there is no

perceived therapeutic benefit beyond that for available drugs). Applications from the most experienced sponsors take an average of 4 months less time to be approved than those from less experienced sponsors.

Priority status and sponsor experience are also the two factors that predict the likelihood that an NDA will be approved. Priority NDAs are four times more likely to be approved than standard NDAs. Applications submitted by the most experienced sponsors are three times more likely to be approved than those submitted by the least experienced companies.

Finally, the limited comparable data available on review time for FDA and the counterpart agency in the United Kingdom paint a more ambiguous picture than that presented in many recent reports. In fact, the latest data published by the regulatory agency in the United Kingdom show that it does not have faster approval times than FDA.

Our Analysis

FDA received 905 NDAs in 1987-94. The total number of NDAs fell from 1987 but remained relatively stable in the ensuing years through 1994 (with the exception of the uncharacteristically small number of submissions in 1993). The number of NDAs for new molecular entities (NMEs) and priority NDAs remained relatively stable over the years.[5] Overall, 17 percent of the NDAs were for priority drugs. (See table 1.)

Table 1: Number of NDAs Submitted 1987-94[a]

Type	1987	1988	1989	1990	1991	1992	1993	1994	Total
All NDAs	142	129	117	99	110	103	87	118	**905**
Priority NDAs	18	20	16	21	21	23	14	19	**152**
NMEs	29	33	32	29	37	34	34	37	**265**

[a]Thirty-six percent of the NMEs are classified as priority applications, 9 percent of non-NMEs.

A large percentage of the applications were not approved. Only 390 of the 700 NDAs submitted through 1992 had been approved by May 16, 1995. In other words, 44 percent of the applications submitted were for drugs that FDA did not find to be safe and effective or that sponsors chose not to pursue further. NMEs were approved at a higher rate than non-NMEs (64 percent to 52 percent), and priority drugs were approved more often

[5]Data on NDAs are often presented separately for NMEs (which are drugs with active components that are new) and for priority drugs because these NDAs may require a different type of review than other NDAs. The types of NDAs that are classified as non-NMEs are listed in appendix I.

than standard drugs (76 percent to 52 percent). This means that whether an NDA is or is not ultimately approved is as relevant a question as how long approval takes.[6] (See table 2.)

Table 2: Final Status of NDAs Submitted 1987-92[a]

Type	Approved	Withdrawn	Refused	Approvable	Not approvable
NDA					
NMEs	64%	18%	2%	3%	12%
Non-NMEs	52	22	8	3	15
Priority	76	14	0	0	10
Standard	52	22	7	3	15
Sponsor					
Most experienced group	63	22	3	3	9
Least inexperienced group	41	17	15	2	25
All	56	21	6	3	14

[a]Final status as of May 16, 1995. All rows sum to 100 percent except for rounding.

The data in table 2 show that NDAs that are submitted by experienced sponsors and priority NDAs are more likely to be approved than standard NDAs or NDAs submitted by sponsors with little experience with the process. These results are supported by a regression analysis that shows that both the NDA's priority and the sponsor's experience are statistically significant predictors of outcome (see appendix I for our definition of sponsor experience and appendix V for the regression analysis). The regression analysis found that, statistically controlling for the effects of the other explanatory variables in the model, priority NDAs are four times more likely to be approved than standard NDAs and that applications submitted by the most experienced companies are three times more likely to be approved than those submitted by less experienced sponsors.

How Long Does the Review Process Take?

Table 3 shows for 1987-92 the average time (in months) from when NDAs were first submitted to when final decisions were made for both NDAs that

[6]Some other studies of the drug review process have reported higher rates of approval. These studies either have looked at subsets of the population of NDAs that have higher approval rates (such as NMEs) or have not included in their calculations applications that FDA refused to file. In contrast, our report of a 56-percent approval rate includes all types of NDAs and all applications listed in FDA's records, even those that FDA refused to file.

were approved and those that were not.[7] The table also distinguishes between all NDAs and those that were approved in three categories: new molecular entities, priority applications, and standard applications.

Table 3: Average Number of Months From Initial NDA Submission to Final Decision for NDAs Submitted 1987-92

	Year of initial submission					
Type	**1987**	**1988**	**1989**	**1990**	**1991**	**1992**
All NDAs	33	31	24	23	21	18
Approved NDAs	33	30	25	25	21	19
All NMEs	31	32	21	21	25	20
Approved NMEs	33	26	23	23	23	21
All priority	29	29	16	23	17	17
Approved priority	23	23	16	22	18	16
All standard	34	32	26	23	21	18
Approved standard	35	32	28	27	22	20

As can be seen from the table, the processing time for all eight categories of NDAs fell considerably (from 33 to 18 months, or 45 percent, for all NDAs, or from 33 to 19 months, or 42 percent for approved NDAs). In addition, the reductions in time came for NDAs submitted throughout the period of our study. This finding is consistent with FDA's statements that review time has decreased in recent years.

Alternative presentations of the data demonstrate the same result. For example, table 4 shows that the number of months that passed before half of all submissions were approved declined from 58 months for NDAs submitted in 1987 to 33 months for 1992 submissions. Since just 56 percent of the NDAs submitted between 1987 and 1992 were approved, this measure captures the approval period for almost all the approvals that will ultimately be granted.[8] Similarly, table 4 shows that the proportion of submitted NDAs that were approved within 2 years increased from 23 percent for NDAs submitted in 1987 to 39 percent for NDAs submitted in 1992.

[7]The only FDA decision that is truly "final" is the decision to approve the NDA. All other decisions allow the sponsor to continue to pursue an approval decision. For example, even if FDA sends a not-approvable letter, the sponsor can address the concerns listed in that letter and resubmit the NDA. Therefore, whenever we use the term "final decision" in this report, it means the status of the application as of May 16, 1995.

[8]Fifty-eight percent of the NDAs submitted in 1988 and 1991 were approved, the years with the greatest proportion of approvals (see appendix VI).

Table 4: Two Alternative Measures of Review Time for NDAs Submitted 1987-92

Year of submission	Months until half of all NDAs were approved	Percent of NDAs approved within 24 months
1987	58	23%
1988	52	27
1989	41	31
1990	47	29
1991	30	36
1992	33	39

Closer examination of the individual NDAs shows that they differed considerably in how long it took before a final decision was made. Some NDAs were approved within a few months (the shortest was 2 months); others took years (the slowest was 96 months). The variation was similar among applications that were not approved. Some were withdrawn on the day they were submitted. The longest outstanding application was 92 months old.

This considerable variation raises the question of what differentiates one NDA from the next: Do some factors predict the time it will take to reach a final decision? When we tested potential explanatory variables, we found that the priority FDA assigned to an application and the sponsor's experience in submitting NDAs were statistically significant predictors of how long review and approval took. (See appendix IV.) More specifically, controlling for the effects of the other explanatory variables in the model, our regression analysis found that priority NDA applications are approved 10 months faster than standard applications and that applications from the most experienced sponsors are approved 4 months faster than applications from less experienced sponsors.

Process Measures of Time

The interval between first submission and final decision indicates how long the public must wait for drugs after sponsors believe they have assembled all the evidence to support an approval decision. Alternative measures provide insight into what happens to an NDA before FDA approves it. One such measure is the extent to which FDA is "on time" in making decisions. We examined both the degree to which FDA was on time and the factors that influenced whether it made its decisions on time. The criteria for "on time" performance that we used in this analysis were established

under the Prescription Drug User Fee Act of 1992.[9] Although on-time performance may be seen as one indicator of FDA's efficiency, it is important to note that FDA is not required to meet these criteria until 1997.[10]

Of all the decisions FDA made on the NDAs submitted between 1987 and 1993, 67 percent were on time. Simpler decisions (for example, refusals to file) were made on time more often than relatively complex decisions (for example, priority applications in which the first decision was an approval). Overall, the on-time percentage remained relatively stable, varying between a low of 62 percent for NDAs submitted in 1992 and a high of 72 percent for NDAs submitted in 1987.[11] In sharp contrast to the decline in overall time between submission and final decision shown in table 3, this stability shows that there is little relationship between the time FDA takes to reach a final decision and whether or not it meets its deadlines for specific actions.[12]

Another process measure of review time is based on where responsibility lies for different parts of the process—with FDA for the intervals during which it acts on an application, or with the sponsor, for the intervals during which FDA waits for the sponsor to provide additional information or to resubmit the application. Figure 2 shows how their relative times were distributed for approved NDAs submitted between 1987 and 1992.

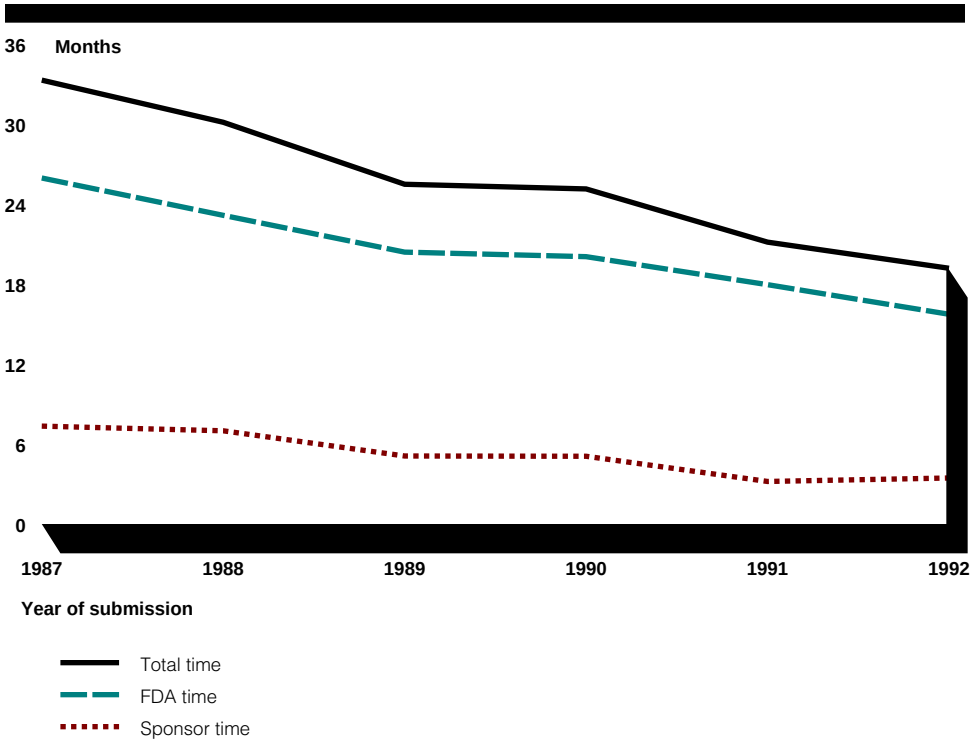
[9]Upon receipt of an NDA, FDA has 60 days to determine whether the application will be filed or refused. If the application is filed, under the performance goals referenced in the Prescription Drug User Fee Act, FDA is to perform a complete review of the entire application and issue an approval letter, approvable letter, or not-approvable letter within 6 months for priority applications and within 12 months for standard applications. In accordance with the act, FDA intends to fully implement these goals by the end of fiscal year 1997.

[10]Our calculations of FDA's on-time performance were conservative, tending to underestimate, rather than overestimate, the proportion of FDA's actions that have been on time (see appendix II).

[11]See appendix II. We excluded the rates for the 1994 cohort from this analysis.

[12]In commenting on a draft of this report, FDA maintained that our on-time analysis underestimates the extent to which its performance has improved. See appendix II for FDA's comments and our response.

Figure 2: FDA and Sponsor Times for Approved NDAs Submitted 1987-92



As can be seen from the figure, sponsors accounted for approximately 20 percent of the time in the NDA phase for applications that FDA approved.[13] Importantly, the time for both sponsors and FDA diminished for NDAs submitted between 1987 and 1992.

Approval Times in the United Kingdom

Regulatory processes similar to FDA's have been mentioned as models for reforming FDA. The one most often mentioned is the United Kingdom's. Proponents of FDA reform have argued that the British counterpart to the FDA, the Medicines Control Agency, performs reviews of equivalent quality and does so significantly more quickly.

Comparisons between the Medicines Control Agency and FDA are difficult because the workload, approval criteria, and review procedures followed by the agency may not be exactly the same as FDA's and because its reports cover a slightly different period than FDA's. However, the most recent data

[13]Our calculations of sponsor time were conservative, tending to underestimate, rather than overestimate, the proportion of review time accounted for by the sponsors of NDAs (see appendix I).

show that overall approval times are actually somewhat longer in the United Kingdom than they are in this country. For the 12-month period ending September 30, 1994, the Medicines Control Agency reported that the median approval time for applications that were apparently equivalent to NMEs was 30 months. The average time was 24 months. The fastest approval was granted in about 4 months, the slowest in 62 months.

According to FDA, the median approval time for NMEs approved in the United States in calendar year 1994 was 18 months, the average about 20 months. The fastest FDA approval took about 6 months and the slowest about 40 months. (See appendix VII for a fuller comparison.)

Conclusion and Implications

Aside from shedding light on the central issue of time, the data we assembled provide some interesting but rarely mentioned facts about FDA's drug review and approval process. First, nearly half the NDAs submitted to FDA are not approved for marketing. The 44 percent of NDAs that were not approved in our sample either were not judged by FDA to be safe and effective or were not pursued by their sponsors. Second, the percentage of NDAs for drugs that are viewed by FDA as offering an important therapeutic advance is relatively small. As we pointed out in table 1, only 17 percent of all NDAs were given priority status. Third, our data on drug review and approval show that approximately one fifth of the time in that process comprises activities for which sponsors are responsible.

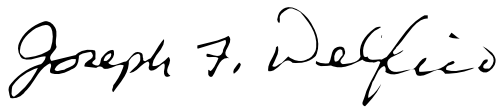
With respect to time, NDAs are moving more quickly through the drug review and approval process. Whether this improvement is because of actions by FDA or the pharmaceutical industry or some other factors is an issue that is beyond the scope of this report. However, the consistency of all our results supports the conclusion that the reduction in time is real and not an artifact of how time is measured. Further, the magnitude of the reduction—more than 40 percent—should be considered in the ongoing discussions of the need to change the NDA review process or the agency in order to speed the availability of drugs to patients.

Agency Comments

FDA officials reviewed a draft of this report and discussed their comments with us. They generally agreed with our analytic methods and findings. However, they expressed concerns about some aspects of our analysis of FDA's on-time performance. These comments, and our responses to them, appear in appendix II. FDA also provided a number of specific technical comments that have been incorporated into the report where appropriate.

As we agreed with your offices, we plan no further distribution of this report until 30 days from its date of issue, unless you publicly announce its contents earlier. We will then send copies to the Secretary of Health and Human Services, the Commissioner of Food and Drugs, and to others who are interested. We will also make copies available to others upon request.

If you have any questions regarding our report, please call me at (202) 512-2900 or George Silberman, Assistant Director, at (202) 512-5885.



Joseph F. Delfico
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Abbreviations

CSM	Committee on the Safety of Medicines
FDA	Food and Drug Administration
GAO	U.S. General Accounting Office
MCA	Medicines Control Agency
NDA	New drug application
NME	New molecular entity

Data and Methodology

The Data We Examined

At our request, FDA provided detailed information about all new drug applications, totaling 905, initially submitted between January 1, 1987, and December 31, 1994. This included the contents and date of all FDA decisions and all major communications between FDA and the NDA sponsors through May 16, 1995. The variables we used in our analysis are described in the next section.

Our choice of this time period has important implications for the analysis of drug review time. First, we started with 1987 because that was the first full year following a major change in FDA's drug review procedures. We do not believe that examining new drug applications from before 1987 would shed any light on FDA's current activities. Second, most reports of drug approval times, including those published by FDA, measure time for drugs approved during a particular period, regardless of when they were submitted. Some approved drugs may have been submitted much earlier. By limiting our analysis to new drug applications submitted (but not necessarily approved) in 1987 and later, we have limited the maximum value of review time. However, we do not believe that this has significantly biased our findings, since relatively few drugs win approval after exceptionally long review periods. (Appendix VI describes the outcomes of the review process as a function of year of approval in our sample.)

While we were unable to independently verify the accuracy of all the data FDA provided, we did undertake a number of validation procedures to ensure the quality of the data. First, we performed extensive checks of the internal consistency of the databases FDA provided. In several cases, we uncovered discrepancies in the level of detail for different categories of drugs and between the information contained in one data file and that contained in another file. We resolved all these inconsistencies with FDA.

Second, we compared the information in the data files with published sources where possible. For approved drugs, many reports (by FDA and by others) list the names, submission dates, and approval dates. We were able to resolve with FDA the few inconsistencies we discovered through this method. However, it is important to note that we were unable to do this for nonapproved drugs because there are no published reports on them.

Third, for an earlier report, we had already obtained documentation for all NDAs for NMEs submitted in 1989.[1] We compared those documents with the

[1]U.S. General Accounting Office, FDA User Fees: Current Measures Not Sufficient for Evaluating Effect on Public Health, GAO/PEMD-94-26 (Washington, D.C.: July 1994).

data FDA provided us for this report, and we were able to resolve all apparent inconsistencies.

The Variables We Analyzed

This section describes the variables we used in our analyses. Our definitions of the variables do not necessarily agree with FDA's practice. FDA provided some of the variables directly to us; we computed others from the data FDA provided and from other sources.[2]

Drug Characteristics

Priority drugs. Those that FDA determines to represent a significant therapeutic advance, either offering important therapeutic gains (such as the first treatment for a condition) or reducing adverse reactions. Nonpriority, or standard, drugs offer no therapeutic advantage over other drugs already on the market.

New molecular entities. Drugs with molecular structures that have not previously been approved for marketing in this country, either as a separate drug or as part of a combination product. Drugs that are not NMEs are from one of six categories defined by FDA: a new ester or salt, a new dosage form or formulation of a previously approved compound, a new combination of previously approved compounds, a new manufacturer of a previously approved drug, a new indication for an already approved drug, or drugs already marketed but without an approved NDA (that is, drugs first marketed before FDA began reviewing NDAs).

Submissions to the Review Process

Initial submission. The first submission of the application to FDA.

Resubmission. After a sponsor has withdrawn an application or FDA has refused it for filing, sponsors can resubmit it.

Major amendments. Substantial submissions of new information by the sponsor to FDA, either of the sponsor's own volition or in response to an FDA query.

Results of the Review Process

Refusal to file. After FDA receives a new drug application, the agency first determines if the application is sufficiently complete to allow a substantive review. If not, FDA can refuse to file it. Since the implementation of user

[2]For more information about the drug approval process, drug characteristics, and measurement of time, see FDA User Fees, esp. pp. 4-10 and app. I.

fees in 1993, applications must be rejected if the sponsor has failed to pay the appropriate fee to FDA. These applications are categorized as "unacceptable for filing," not refusal to file.

Approval. If FDA is satisfied that a drug is safe and effective, it approves the drug for marketing for its intended use as described in the label.

Approvable. FDA determines that a drug is approvable if there is substantial evidence that it is safe and effective, but the sponsor must either supply additional information or agree to some limiting conditions before FDA grants final approval.

Not approvable. If FDA determines that the evidence submitted by the sponsor to show that the drug is safe and effective is insufficient, the agency notifies the sponsor that the drug is not approvable.

Withdrawal. The sponsor of an NDA may withdraw it at any time for any reason.

Final status. We examined the data file for each NDA to see if the drug had ever been approved. If not, we searched the file for the last event that was a withdrawal, not approvable, approvable, or a refusal to file, and we identified that event as the application's final status. However, since FDA never definitively rejects applications, some whose final status is other than approval may ultimately be approved. (See appendix III.)

Drug Review Time

Year of submission. The calendar year in which an application is first submitted to FDA.

Review time. The period between the date of the initial submission of an NDA, even if FDA refuses to file it, and the date of the application's final status in the data file. For approved drugs, review time is the period between the initial submission and the date of approval.

FDA time and sponsor time. For some of the analyses, we divided the total review time into time that is FDA's responsibility and time that is the sponsor's responsibility. FDA time consists of periods that begin when the agency has the information it has requested from the sponsor for that stage of the review and that end when FDA issues a judgment of refusal to file, approval, approvable, or not approvable or the application is

withdrawn.[3] Sponsor time consists of periods when FDA is waiting for the sponsor to provide additional information or to resubmit the application. FDA time and sponsor time are complementary and together sum to total review time.

Review cycles. Each period of FDA time is one review cycle.

FDA's on-time performance. The Prescription Drug User Fee Act of 1992 established specific performance goals for each review cycle.[4] The agency must issue refusals to file within 60 days of submission and must reach all other decisions for priority drugs within 6 months and for standard drugs within 12 months. We applied these guidelines retroactively to identify actions as either on time or not on time for each review cycle for NDAs submitted between 1987 and 1994.

Sponsor Characteristics

Experience. We divided the sponsoring pharmaceutical companies into four groups, based on their activities between 1987 and 1994. We defined the most experienced companies as those that submitted 9 or more NDAs to FDA during this period (that is, at least one per year). Those that submitted between 5 and 8 NDAs in that period made up the middle-experience group. The two least experienced groups submitted 4 or fewer NDAs. We further divided the least experienced companies into one group with affiliations with other companies that sponsored NDAs during this period and another group without such affiliations. Affiliation meant that another sponsoring company had a significant ownership stake in the sponsor of the NDA. We identified affiliations by reviewing business and financial directories.

Methodology

Most of our statistical analyses consist simply of listing average review times, or the number of NDAs with a particular characteristic, separately by year of submission or by the outcome of review. However, we also conducted two regression analyses, one to identify variables related to the

[3]The beginning of a period of FDA time is clear when the NDA is first submitted or resubmitted after a withdrawal or refusal to file. It is less obvious when the sponsor submits amendments in response to approvable or not-approvable letters, because sponsors frequently submit several amendments on different dates. We chose to use the date of the first amendment as starting a period of FDA time, even though FDA may not have all the information it needs to continue the review at that point. Our procedure maximizes FDA time and minimizes sponsor time. An alternative method is to start a period of FDA time when the last amendment before the next FDA action is received, letting FDA review the earlier amendments during a period of sponsor time. That procedure minimizes FDA time and maximizes sponsor time.

[4]See FDA User Fees, esp. pp. 21-22.

length of the review process and another to identify factors related to drug approval. (See appendixes IV and V.) This allowed us to isolate the effects of one variable (for example, drug priority) while statistically holding constant the other predictor variables (for example, year of submission and the experience of the sponsoring company). All our statements about statistical significance are based on the results of the regressions, which answer the question: If there were no differences among these NDAs except, for example, drug priority, does drug priority influence the chances of approval?

We performed our work in accordance with generally accepted government auditing standards.

Alternative Measures of Time

The key statistics presented in this report are the average times to final decisions for NDAs submitted in consecutive calendar years from 1987 onward. Previous reports on time have presented other results, sometimes relying on slightly different measures of time, sometimes reporting other statistics (medians rather than averages), and usually constructing cohorts based on the years in which the NDAs were approved rather than the years in which they were submitted. In the sections that follow, we place our work in the context of other studies of drug review and approval time by examining the differences in approach.

Starting Points for Calculations of Time

In our study, review time begins with the first submission of the NDA to FDA. In FDA's statistical reports, it starts the clock with the submission of an "accepted" NDA. The two measures would provide similar results if the NDA were accepted on the first submission or, if FDA refused to file it, the sponsor never resubmitted the application. However, in any situation in which FDA refused to file the NDA and the sponsor eventually resubmitted it, our measure of review time would be longer by the interval between the first submission and the date of an accepted submission. Approximately 1 in 10 NDAs (9.4 percent) fall into this category. The average time to resubmission for these applications was a little less than 2 months (1.7 months). Therefore, our review times are slightly longer on average than those reported by FDA.

On-Time Performance

Another approach to time measurement is to be less concerned with how long the process took than with whether it was completed within a specified period. FDA takes this approach when it reports the extent to which the agency meets its user fee performance goals as referenced in the Prescription Drug User Fee Act. Data on our measure of on-time performance appear in the body of this report. Table II.1 shows an annual breakdown of "on time" performance.[1]

[1]See appendix I for a discussion of our coding of an action as on time.

Table II.1: Actions Taken on Time by FDA for NDAs Submitted 1987-94[a]

Year of submission	Number of NDAs	Number of actions	Percent taken "on time"
1987	142	304	72%
1988	129	251	68
1989	117	206	67
1990	99	179	62
1991	110	188	63
1992	103	161	65
1993	87	116	72
1994	118	67	94

[a]Actions taken as of May 16, 1995.

As can be seen from table II.1, the percentages have changed little over the years.[2] Interestingly, this is in contrast to the reduction in total review time (the entire interval between submission and approval) during this period. Seemingly, FDA has managed to reduce the overall time even though it has not increased the proportion of specific actions taken on time.[3]

Agency Comments and Our Response

In commenting on a draft of this report, FDA officials agreed with our general conclusions but made two points regarding our analysis of on-time performance.

First, FDA emphasized that the 6- and 12-months guidelines used in our analysis were not in effect during the years we studied and that FDA is not required to meet them until 1997.

Second, while FDA believes that its review cycle on-time performance may not have improved, the agency cautioned that the nature of its actions has changed with the initiation of the user fee program, particularly for not-approvable letters. Prior to the initiation of user fees, not-approvable letters were not necessarily a complete listing of all the deficiencies in the

[2]The data for 1994 are biased by the small number and type of decisions that had been made for those NDAs by the time we collected our data.

[3]The assumptions we used to calculate on-time performance served to minimize the proportion of FDA actions that met the standard. First, as we described in appendix I, we started each period of FDA time with the submission of the first amendment after the last FDA action, not the submission of the last amendment. Second, we did not extend the deadline by 3 months if major amendments were filed close to the original due date, as allowed in some circumstances under user fees. We reported that 67 percent of FDA's actions are on time. Choosing assumptions that are the most favorable to FDA (starting the clock with the last submitted amendment and extending the deadline by 3 months in every case) would increase this figure to 78 percent.

NDA. For example, FDA may have sent one not-approvable letter when the review of one section of the NDA was complete and additional not-approvable letters as other sections of the review were completed. After user fees, FDA is required to take complete actions, so a not-approvable letter must contain all the deficiencies FDA identifies. In other words, FDA must now complete more work to satisfy a post-user fee deadline than it had to before user fees were introduced.

We agree with FDA's first point. FDA's second point argues for caution in making comparisons of on-time performance between different years. We agree that changes in procedure would invalidate such comparisons. For that reason, we did not use this measure as an indicator of whether the overall timeliness of the drug approval process had improved. Rather, we included the trends in on-time performance in the report in order to be comprehensive in presenting all measures of time that others had reported.

Alternative Measures of Total Review Time

Average Times Compared to Median Times

Throughout this report, we have reported the average times for NDA review. An alternative is to report the median review time, the time for the 50th percentile application. In this case, medians reduce the influence of drugs with unusually long review periods and are therefore usually somewhat lower than average review times. Table II.2 lists the average and median approval times for the drugs we examined by year of submission. While the median values are generally slightly lower, they show the same pattern of consistent decrease as the average values.

Table II.2: Average and Median Months to Approval for NDAs Submitted 1987-92

Year of submission	Average	Median
1987	33.3	29.1
1988	30.1	26.7
1989	25.5	23.4
1990	25.1	23.1
1991	21.1	21.3
1992	19.2	18.7

Year of Submission Compared to Year of Approval

FDA and others frequently report time statistics for NDAs that group the applications by the year in which they were approved rather than the year in which they were submitted. To some extent, this reflects FDA's general orientation away from publishing data on submissions (given that much of that information is proprietary until they are approved). Table II.3 compares the average approval times we computed using year of submission with the average approval times FDA computed using year of decision. The discussion that follows the table indicates why grouping NDAs by year of submission is preferable for our purpose.

Table II.3: Average NDA Approval Times in Months, 1987-94

Year	By year of submission[a]	By year of approval[b]
1987	33.3	29.0
1988	30.1	28.9
1989	25.5	30.9
1990	25.1	30.0
1991	21.1	28.5
1992	19.2	32.6
1993	[c]	33.1
1994	[c]	25.5

[a]Calculated by GAO.

[b]Reported by FDA.

[c]We do not present values for these years because they may be biased as a result of the censoring problem discussed in appendix VI.

Table II.3 shows an obvious difference between the decrease in approval times when NDAs are grouped by year of submission and the stability when they are grouped by year of approval. This difference arises because grouping by year of approval incorporates into the calculation whatever backlog of NDAs existed at FDA. For example, several NDAs submitted in 1987 that had very lengthy 5-year reviews would increase the average review time in 1987 for year-of-submission statistics but would add to the average review time in 1992 for year-of-approval figures.

Thus, whenever the possibility of a backlog exists, basing time on year of approval is a less appropriate way to measure current practice because it incorporates the older applications. In contrast, time based on year of submission eliminates the confounding effects of the backlog and,

therefore, is the preferable measure for assessing the current performance of the agency.

In 1987, the first year in our study, FDA had a considerable backlog of NDAs submitted in 1986 and earlier and that backlog affected times throughout nearly the entire period of our study. This can be seen from table II.4.

Table II.4: Percent of NDAs Approved 1987-94 With Approval Times Greater Than 4 Years

Year of approval	Total NDAs approved	Percent approved in more than 4 years
1987	68	15%
1988	67	15
1989	87	20
1990	64	16
1991	63	16
1992	91	23
1993	70	24
1994	62	10

Source: Adapted from FDA statistics.

As the table shows, a considerable proportion of the approvals in every year except for 1994 were for older NDAs that had been under review for a long time. The first years in which FDA seemed to make progress in reducing the backlog were 1992 and 1993, when larger percentages of older applications were approved. This progress was reflected in the smaller percentage of older NDAs that were approved in 1994 and in the sharp drop in times measured by year of approval between 1993 and 1994 (see table II.3). The decrease from 33 to 26 months indicates that the backlog may have finally passed through the system.

Intermediate Outcomes From FDA's Review Process

In this appendix, we present data on what happens to the NDAs as they move through the review process, focusing on three kinds of activities: first actions, review cycles, and major amendments.

First Actions

Table III.1 shows the first action taken on NDAs submitted in each successive year. It can be seen that approval is the initial decision for relatively few NDAs.

Table III.1: First Actions on NDAs Submitted 1987-94

	Year of submission							
First action	**1987**	**1988**	**1989**	**1990**	**1991**	**1992**	**1993**	**1994**
Percent of first actions on submissions[a]								
Refusal to file	16%	10%	6%	13%	24%	27%	18%	11%
Withdrawal	13	18	17	15	8	13	8	4
Not approvable	46	41	37	34	32	19	20	10
Approvable	12	13	19	19	16	22	15	4
Approval	13	18	21	18	19	17	17	4
No first action[b]	0	0	0	0	1	1	11	52
Total	**100%**	**100%**	**100%**	**99%**	**100%**	**99%**	**89%**	**86%**
Total number of submissions	**142**	**129**	**117**	**99**	**110**	**103**	**87**	**118**

[a]Percentages may not total 100 because of rounding. Percentages for 1993 and 1994 do not total 100 because NDAs found "unacceptable for filing" because of failure to pay user fees are not included in the table.

[b]As of May 16, 1995.

Given that approximately 55 percent of all NDAs are ultimately approved, the data in table III.1 also show that such "negative" decisions as refusal to file, not approvable, and withdrawal are not necessarily fatal to an application. Of the 110 NDAs submitted from 1987 to 1992 that FDA initially refused to file, 35 (32 percent) were ultimately approved. Similarly, 43 percent of the NDAs that had a not-approvable first action were ultimately approved, and 27 percent of the withdrawals were resubmitted and approved. Overall, 43 percent of the 390 drugs submitted from 1987 to 1992 that were approved were refused, withdrawn, or found not approvable at some point on their way to approval.

Cycles

FDA reports the review cycles that an NDA goes through in its yearly Statistical Reports. A cycle starts with the submission or resubmission of an NDA and ends with the withdrawal of the NDA, a refusal to file decision, or an approval, approvable, or not-approvable letter. Each new cycle starts the review clock anew. Table III.2 shows the number of cycles for various types of NDAs.

Table III.2: Review Cycles for NDAs Submitted 1987-92

	Number of cycles					
					Average	
Type of NDA	1	2	3	≥4	Total	Approved only
Approved[a]	32%	41%	19%	9%	2.1	[b]
Not approved	64	22	11	3	1.5	[b]
Priority	52	38	7	4	1.6	1.7
Standard	45	31	17	7	1.9	2.2
NME	54	38	7	2	1.6	1.7
Non-NME	43	30	18	9	2.0	2.3
Year of submission						
1987	32	35	25	8	2.1	2.4
1988	47	29	15	10	1.9	2.2
1989	51	30	14	5	1.8	2.0
1990	48	34	9	8	1.8	2.1
1991	49	34	14	4	1.7	2.0
1992	55	33	11	1	1.6	1.9
All	46	33	15	6	1.8	2.1

[a]Percentages may not total 100 because of rounding.

[b]Not applicable.

As can be seen from table III.2, some types of NDAs are more likely to go through multiple review cycles than others. Approved NDAs go through more cycles on average than applications that get dropped along the way; priority NDAs go through fewer cycles on average than standard NDAs; and, similarly, NMEs go through fewer cycles on average than non-NMEs. The number of cycles for both approved NDAs and all NDAs has decreased for submissions since 1987. This decrease is consistent with the decrease in time to final decisions.

Amendments

FDA has questions about almost all NDAs and requires sponsors to submit additional data in response to those questions. The sponsors submit these data in the form of amendments. Relatively small amounts of data (for example, clarification of a point or correction of a value) are classified as minor amendments, and relatively large amounts of data (for example, a reanalysis or results of an additional study) are classified as major amendments.

Table III.3: Major Amendments for NDAs Submitted 1987-92

	Number of major amendments					
					Average	
Type of NDA	0	1-5	6-10	≥11	Total	Approved only
Approved[a]	12%	73%	12%	3%	3.5	[b]
Not approved	45	49	5	1	1.7	[b]
Priority	23	57	17	3	3.3	3.5
Standard	28	63	7	2	2.6	3.5
NME	20	59	15	5	3.8	4.6
Non-NME	29	63	6	1	2.3	3.0
Year of submission						
1987	25	63	8	4	2.9	4.3
1988	20	71	6	2	2.7	3.1
1989	25	59	15	1	3.1	3.8
1990	31	54	10	5	2.9	4.4
1991	34	55	9	2	2.5	2.9
1992	27	69	4	0	2.0	2.3
All	27	62	9	2	2.7	3.5

[a]Percentages may not total 100 because of rounding.

[b]Not applicable.

Table III.3 shows the number of amendments for different types of NDAs. As expected, NDAs that are pursued through to approval have more major amendments on the average than NDAs that drop out of the process. NDAs for priority drugs and for NMEs required more amending on average than applications for standard drugs and non-NMEs. As with the data on cycles, table III.3 shows a decrease in the number of amendments for submissions since 1987.

These data, along with those in table III.1 showing a steady decrease in the numbers of not approvables and in table III.2 showing fewer cycles,

suggest that the drug review and approval process is getting "cleaner." This change may result from different applications submitted by the sponsors of new drugs, different FDA review procedures, or both. Without additional study, it is not possible to identify the reasons for this. However, all three sets of data (on first action, cycles, and major amendments) are consistent with a quicker review process.

Regression Analyses for Review Time

We conducted two regression analyses predicting review time, one for approved new drug applications and the other for applications that were not approved. As table IV.1 shows, we found that the length of time until approval was significantly affected by three factors—year of submission, drug priority, and sponsor experience. Applications submitted in later years were approved much faster than earlier applications (for example, 11 months quicker in 1992 than in 1987). Drug applications given therapeutic priority by FDA were approved nearly 10 months faster than standard drugs. Applications from sponsors that submitted many NDAs were approved more quickly than applications from relatively inexperienced sponsors (for example, applications from the most experienced sponsors were approved 4 months faster than those from inexperienced sponsors that were not affiliated with other sponsoring companies).

Table IV.1: For Approved New Drug Applications, Regression Analysis Predicting Number of Months From First Submission to Approval[a]

Variable[b]	Coefficient[c]	T-value[d]	Probability level[e]	Sample mean
Year of submission (vs. 1987)				
1988	–2.44	–1.08	.28	.19
1989	–6.92	–2.95	.01	.17
1990	–6.54	–2.60	.01	.14
1991	–11.19	–4.76	.01	.16
1992	–11.39	–4.54	.01	.14
Priority drugs (vs. standard)	–9.89	–4.97	.01	.23
New molecular entity (vs. not)	.38	.22	.82	.32
Sponsor experience (vs. inexperienced, unaffiliated)				
Inexperienced, affiliated	–6.47	–1.99	.05	.07
Mid-experienced	–4.14	–1.58	.12	.12
Most experienced	–4.38	–2.22	.03	.65
Constant	38.25			

[a]For applications first submitted from 1987 to 1992, N = 390, and R-squared = 0.24. The mean review time is 26.36 months.

[b]The list of predictor variables also included categorical variables for the FDA reviewing divisions. We did not report those coefficients here because they cannot readily be interpreted; the chemical and therapeutic content and complexities of new drugs are strongly correlated with the reviewing divisions, making it impossible for us to distinguish the effects of drug variations from those that are attributable to the internal operations of the divisions. However, it is important to note that the coefficients reported in the table are statistically independent of the effects of the reviewing division.

[c]Coefficients are from an ordinary least-squares regression analysis with the SAS-PC software package. The coefficient indicates the change in review time relative to that of the group left out. For example, the coefficient of –2.44 for applications submitted in 1988 means that those applications were approved nearly 2-1/2 times faster than applications submitted in 1987, the group left out.

[d]The T-values test the statistical significance of the coefficients.

[e]Probability level refers to the chances that the coefficient equals zero in the population. By convention, coefficients with a probability level less than or equal to 5 percent (0.05) are regarded as statistically significant. In this table, 0.01 indicates a probability level less than or equal to 0.01.

In contrast, for drugs that were not approved, the only significant factor was year of submission. Applications submitted in later years were acted on more quickly than those submitted earlier (see table IV.2). Neither therapeutic priority nor the experience of the sponsor affected review

time. It is important to reiterate that FDA does not definitively reject applications it does not approve. Therefore, FDA may take further action on some of the applications in this analysis.

Table IV.2: For New Drug Applications Not Approved, Regression Analysis Predicting Number of Months From First Submission to Date of Final Action[a]

Variable[b]	Coefficient[c]	T-value[d]	Probability level[e]	Sample mean
Year of submission (vs. 1987)				
1988	.98	.27	.79	.18
1989	–10.13	–2.67	.01	.17
1990	–12.83	–3.32	.01	.15
1991	–11.90	–3.01	.01	.15
1992	–15.87	–4.14	.01	.16
Priority drugs (vs. standard)	2.79	.71	.48	.09
New molecular entity (vs. not)	1.90	.68	.50	.22
Sponsor experience (vs. inexperienced, unaffiliated)				
Inexperienced, affiliated	7.10	1.51	.13	.07
Mid-experienced	2.01	.53	.59	.14
Most experienced	4.00	1.53	.13	.48
Constant	34.70			

[a]For applications first submitted from 1987 to 1992, N = 308, and R-squared = 0.16. Mean review time is 24.93 months.

[b]The list of predictor variables also included categorical variables for the FDA reviewing divisions. We did not report those coefficients here because they cannot readily be interpreted; the chemical and therapeutic content and complexities of new drugs are strongly correlated with the reviewing divisions, making it impossible for us to distinguish effects from drug variations from those that are attributable to the internal operations of the divisions. However, it is important to note that the coefficients reported in the table are statistically independent of the effects of the reviewing division.

[c]Coefficients are from an ordinary least-squares regression analysis with the SAS-PC software package. The coefficient indicates the change in review time relative to that of the group left out. For example, the coefficient of 0.98 for applications submitted in 1988 means that those applications were acted on nearly 1 month slower than applications submitted in 1987, the group left out.

[d]The T-values test the statistical significance of the coefficients.

[e]Probability level refers to the chances that the coefficient equals zero in the population. By convention, coefficients with a probability level less than or equal to 5 percent (0.05) are regarded as statistically significant. In this table, 0.01 indicates a probability level less than or equal to 0.01.

Regression Analysis for Approval

Table V.1 presents the results of a logistic regression analysis predicting NDA approval. The outcome variable is dichotomous: "1" indicates that the drug has been approved, "0" that it has not been approved. Fifty-six percent of the NDAs were approved. The data set for the regression consists of the 698 drugs first submitted between 1987 and 1992 that had final status values as of May 16, 1995 (two applications were pending).

Table V.1: Logistic Regression Analysis Predicting NDA Approval

Variable[a]	Coefficient[b]	Odds ratio[c]	Chi-square[d]	Probability level[e]	Sample mean
Year of submission (vs. 1987)					
1988	.06	1.07	.06	.81	.18
1989	-.18	.84	.43	.51	.17
1990	-.30	.74	1.07	.30	.14
1991	.01	1.01	.01	.98	.16
1992	-.46	.63	2.62	.11	.15
Priority drug (vs. standard)	1.30	3.68	23.98	.01	.17
New molecular entity (vs. not)	.27	1.30	1.70	.19	.28
Sponsor experience (vs. inexperienced, unaffiliated)					
Inexperienced, affiliated	.49	1.63	1.83	.18	.07
Mid-experienced	.60	1.81	4.03	.04	.13
Most experienced	1.10	3.01	28.21	.01	.57
Constant	-.49				

[a]The list of predictor variables also included categorical variables for the FDA reviewing divisions. We did not report those coefficients here because they are not readily interpretable; the chemical and therapeutic content and complexities of new drugs are strongly correlated with the reviewing divisions, making it impossible for us to distinguish effects from drug variations from those that are attributable to the internal operations of the divisions. However, it is important to note that the coefficients reported in the table are statistically independent of the effects of the reviewing division.

[b]Coefficients are from a logistic regression analysis with the SAS-PC software package.

[c]The odds ratio is the exponentiated coefficient ($e^{coefficient}$). The odds ratio indicates the change in the odds of approval relative to that of the group left out. For example, the approval odds for applications submitted in 1988 are 1.07 greater than those for applications submitted in 1987, the group left out.

[d]The chi-square values test the statistical significance of the coefficients.

[e]Probability level refers to the chances that the coefficient equals zero in the population. By convention, coefficients with a probability level less than or equal to 5 percent (0.05) are regarded as statistically significant. In this table, 0.01 indicates a probability level less than or equal to 0.01.

The regression uncovered two statistically significant factors—drug priority and sponsor experience. Priority drugs were approved at nearly four times the rate of nonpriority drugs. Applications from sponsors that submitted many NDAs during this period were approved more often than applications from relatively inexperienced sponsors (applications from the most experienced sponsors were approved three times more often than applications from inexperienced sponsors that were not affiliated with other sponsoring companies; applications from companies with mid-levels of experience were approved nearly twice as often).

Censoring Bias

As mentioned in appendix II, basing our selection of NDAs for analysis on the year of submission has one significant advantage over the more traditional approach of examining NDAs by year of approval. That is, our approach avoids the contamination of the averages by whatever backlog exists. However, relying on year of submission can introduce another form of bias in that averages for approval time computed from all the 1993 and 1994 cohorts incorporate only a highly selective group of NDAs from those 2 years.

As table VI.1 shows, the final status distribution for NDAs submitted in 1993 and 1994 is radically different from that for NDAs submitted earlier. Clearly, this is because many of the applications had not had time to "mature" by the time we collected our data. While more than 50 percent of NDAs submitted in every year from 1987 to 1992 were approved by May 1995, comparatively few of the NDAs submitted in 1993 and 1994 had been approved. Most importantly, the only NDAs from 1993 and 1994 that were approved were those that had been approved relatively quickly. As a result, the average approval time for NDAs submitted in 1987-92 is 26.4 months, while the average time for approved NDAs submitted in 1993 and 1994 is 12.6 months. Because of this bias, we excluded NDAs submitted after 1992 whenever we examined final status.

Table VI.1: Final Status for NDAs Submitted by Year of Submission 1987-94[a]

	Year of submission							
Final status	**1987**	**1988**	**1989**	**1990**	**1991**	**1992**	**1993**	**1994**
Approved	56%	58%	56%	54%	58%	52%	33%	5%
Withdrawn	21	26	22	25	11	18	11	6
Refused to file	7	3	3	3	12	9	11	13
Approvable	1	2	2	3	5	5	7	4
Not approvable	14	12	17	15	13	16	23	11
Pending	0	0	0	0	1	1	11	51

[a]Final status as of May 16, 1995. Percentages may not total 100 because of rounding. Percentages for 1993 and 1994 do not total 100 because NDAs found "unacceptable for filing" because user fees were not paid are not included in the table.

However, we included NDAs from 1991 and 1992 because we found no evidence that including these years risks exposure to the censoring bias found in 1993 and 1994. As table VI.1 shows, the approval rates for 1991 and 1992 are equivalent to those from earlier years. That is, almost all the NDAs from 1991 and 1992 for which approval ultimately would be expected

have already been approved by FDA. Approval times for those years are not likely to increase much.

The question that remains is whether the trend in decreasing time that we observed for submissions between 1987 and 1992 continued for 1993 and 1994 submissions. That question cannot be answered definitively until the 1993 and 1994 cohorts have had time to mature. However, preliminary evidence suggests that the trend continues. Table VI.2 compares the percentage of all applications submitted before 1993 that were approved quickly to the same percentage for NDAs submitted in 1993 and 1994.

Table VI.2: Percent of NDAs Approved Quickly, 1987-92 and 1993-94

Time between acceptance of NDA and approval	1987-92	1993-94
Within 6 months	1%	2%
Within 9 months	4	5
Within 12 months	8	9

As table VI.2 shows, approximately the same percentages of NDAs were approved quickly both before and after 1992. From this evidence, we have no reason to suspect that the trend of speedier drug approval for 1987-92 submissions was reversed for 1993-94 submissions.

Approval Times in the United Kingdom

The United Kingdom's equivalent of FDA is the Medicines Control Agency (MCA). MCA publishes information similar to that contained in FDA's statistical reports, including data on workload (number and type of submissions) and time (how long it takes to review applications). MCA's 1994-95 annual report indicates that the assessment of an application for a new active substance (the apparent equivalent of what FDA terms a new molecular entity) took an average of 56 working days. This figure stands in sharp contrast to FDA's reports that show an average approval time of 20 months for applications for NMEs approved in 1994. No doubt, the sharp contrast in these two averages is one factor creating the impression that approval times are much shorter in the United Kingdom than they are in this country.

However, closer examination of the data in MCA's annual report shows that they should be compared to our data on FDA with caution. Most importantly, the drug review process in the United Kingdom is very different from that in the United States. In the United Kingdom, MCA's assessment is only the first step in a multistage process of drug review and approval. All applications for new active substances are also automatically referred to a government body called the Committee on the Safety of Medicines (CSM). CSM's expert subcommittees also assess the application, and these assessments, along with those from MCA, are provided to CSM. CSM then provides advice to the Licensing Authority, which actually grants or denies the product license. However, the rate of rejection of applications or requests for modifications or additional information is very high (99 percent for applications submitted 1987-89), although many of these issues are minor and quickly resolved. Applications with remaining unresolved issues then go through a formal appeals process that may involve additional work on the part of the applicant, reassessment by MCA or CSM, and, in rare cases, the involvement of another body called the Medicines Commission. Thus, the total time until the license is actually granted is considerably longer than the period of initial assessment by MCA. In contrast, the time FDA reports includes all the steps between an accepted NDA and the final decision on it.

When one examines total time for both processes, the United Kingdom does not appear to be dramatically faster than the United States. One recent study compared approval times for 11 drugs that were approved in both countries during the period 1986-92. The median time in the United States (about 23 months) was 15 percent longer than the median time in

the United Kingdom (20 months).[1] The most recent data from MCA show that overall approval times are actually somewhat longer than that.[2] These data indicate that MCA granted licenses for applications representing 32 new active substances during the 12-month period ending September 30, 1994. The median time for granting a license was 30 months and the average was 24 months. The fastest license was granted in about 4 months, the slowest in 62 months.[3]

FDA's data for the calendar year ending December 31, 1994, indicate that the agency approved a total of 22 new molecular entities. The median approval time was 18 months, average approval time about 20 months. The fastest approval reported by FDA took about 6 months and the slowest about 40 months.

Thus, the most recent data show that approval times for NMEs are actually shorter in the United States. In addition, a broader perspective shows that approval processes in many industrialized nations may be converging.[4] Approval times over the past 10 years for France, Germany, Japan, the United Kingdom, and the United States all seem to be moving toward the 2-year point. The trend in the United States (which had lengthy times throughout the mid-1980s) has been toward more rapid times, whereas the process has been getting slower in some of the other (originally faster) countries.

[1]C. Harvey et al., "A Comparison of the Review of a Cohort of NCEs by Four National Regulatory Authorities," Journal of Pharmaceutical Medicine, 3 (1993), 65-75.

[2]From the bimonthly newsletter of the Medicines Control Agency, The MAIL, November-December 1994.

[3]An additional complication is that MCA was starting to make the conversion to a European-wide drug review process during this period, meaning that the times MCA reported for 1994 may not be typical.

[4]Neal McAuslane, "A Comparison of Regulatory Review Times in Europe, Japan, and the United States," presented at the 31st Annual Meeting of the Drug Information Association, Orlando, Florida, June 26, 1995.

Major Contributors to This Report

This report was prepared by Martin T. Gahart, Michele Orza, George Silberman, and Richard Weston of the Program Evaluation and Methodology Division.

Related GAO Products

FDA User Fees: Current Measures Not Sufficient for Evaluating Effect on Public Health (GAO/PEMD-94-26, July 22, 1994).

FDA Premarket Approval: Process of Approving Lodine as a Drug (GAO/HRD-93-81, April 12, 1993).

FDA Regulations: Sustained Management Attention Needed to Improve Timely Issuance (GAO/HRD-92-35, February 21, 1992).

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