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FDA REVIEW AND APPROVAL TIMES

Statement of Mary R. Hamilton, Ph.D.
Director of Program Evaluation
in the Human Services Area
Program Evaluation and Methodology Division

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Dear Madam Chairman:

In October 1995, GAO issued a report to you on FDA's drug review and approval times.[1] It is a pleasure to appear before this committee today to present our principal findings from that report. My testimony today focuses on two questions you posed when you asked us to appear at today's hearing:

- Has the timeliness of the review and approval process for new drugs changed in recent years?
- How do approval times in the United States compare to approval times in the United Kingdom?

In sum, our conclusions are that new drug applications are moving more quickly through the review and approval process and that the amount of time to obtain an approval is approximately the same in this country and in the United Kingdom.

You also asked that we be prepared to discuss two other related GAO reports, one on FDA review times for medical devices and one on the approach to medical device review in Europe.[2]

Briefly, our work on FDA review times for medical device applications showed that they varied widely from one year to the next. For all types of applications, the median review time increased dramatically in either 1992 or 1993 and then began to decrease. Whether the downturn will continue will only become clear as data for additional years become available.

Our examination of the new systems implemented by the European Union in 1995 for drug and medical device review was initiated at your request. Some aspects of the new systems are seemingly quite distinct from FDA's approach to medical product review, and there is great optimism within the European community about their prospects. However, at this time, it is still too early to know whether the approach the EU has adopted will result in more efficient review while ensuring product safety.

[1]U.S. General Accounting Office, FDA Drug Approval: Review Time Has Decreased in Recent Years, GAO/PEMD-96-1 (Washington, D.C.: October 1995).

[2]U.S. General Accounting Office, Medical Devices: FDA Review Time, GAO/PEMD-96-2 (Washington, D.C.: October 1995), and our forthcoming report on medical device review in the European Union.

Let me turn now to the focus of my testimony today—FDA drug review. First, let me describe FDA's review and approval process and give an overview of our methodology in studying that process.

Background

The process of bringing a drug to market is lengthy and complex and begins with laboratory investigations of the drug's potential. For a drug that seems to hold promise, preclinical animal studies are typically conducted to see how it 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 has been submitted to FDA. As the clinical trials progress through several phases aimed at establishing safety and efficacy, the manufacturer develops the processes that will be 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 a new drug application (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, however, of withdrawing the application at any time.

Methodology

For each NDA submitted between 1987 and 1994 (a total of 905), 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.

We computed time by measuring the interval between all significant events. 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." 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.[3] 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.[4]

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, nor did we study the phase that follows a drug's approval, during which additional studies can be conducted and 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. 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 (on display) shows, the overall decrease in approval times was achieved through gradual reductions in time for applications submitted in each successive year.

[3]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.

[4]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.

The priority that 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.

The data available on review time for FDA and the counterpart agency in the United Kingdom are limited, but show that times are not faster in the UK.

Our Analysis

As mentioned above, 905 NDAs were submitted to FDA in the years 1987-94. Of these, approximately 1 in 5 NDAs (17 percent) were for priority drugs. The other NDAs were for drugs that FDA considered to offer little therapeutic benefit beyond that already available to patients.

Because there has been so much discussion of how long it takes to obtain approval for an NDA, it can be easily missed that in fact many NDAs do not ultimately get approved. Table 1 shows the final status of those NDAs as of May 1995.

Table 1: Final Status for NDAs Submitted, 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.

As can be seen from the table, a relatively large percentage of 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. Truely innovative drugs (known as new molecular entities or NMEs) were approved at a higher rate than non-NMEs (64 percent to 52 percent), and priority drugs were approved more often 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.[5]

How Long Does the Review Process Take?

Table 2 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 were approved and those that were not.[6] The table also distinguishes between all NDAs and those that were approved in three categories: new molecular entities, priority applications, and standard applications.

Table 2: Average Number of Months From Initial NDA Submission to Final Decision, 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 NDA categories fell considerably (45 percent for all NDAs and 42 percent for approved applications). 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.

[5]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.

[6]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.

Alternative presentations of the data demonstrate the same result. For example, table 3 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 approvals that are ever likely to be granted.[7] Similarly, table 3 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.

Table 3: Two Alternative Measures of Review Time, 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). Among applications that were not approved, the variation was similar. 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. 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

[7]Fifty-eight percent of the NDAs submitted in 1988 and 1991 were approved, the years with the greatest proportion of approvals.

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 (using criteria established under the Prescription Drug User Fee Act).[8] We examined both the degree to which FDA was on time and the factors that influenced whether it made its decisions on time.[9]

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.[10] 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.[11]

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 (on display) shows how their relative times were distributed for approved NDAs submitted between

[8]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.

[9]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. In addition, our criteria for determining whether the agency was "on-time" were based on the performance goals contained in the Prescription Drug User Fee Act of 1992.

[10]We excluded the 1994 data.

[11]In commenting on our October 1995 report on review time, FDA maintained that our on-time analysis underestimates the extent to which its performance has improved.

1987 and 1992. Sponsors accounted for approximately 20 percent of the time in the NDA phase for applications that FDA approved.[12] Importantly, the time for both sponsors and FDA diminished for NDAs submitted between 1987 and 1992.

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. In the United Kingdom, MCA's assessment is only the first step in the process of drug review and approval. All applications for new active substances are also referred to a government body called the Committee on the Safety of Medicines (CSM). CSM's expert subcommittees also assess the application and then send these assessments, along with those from MCA, to the full committee. CSM then makes a recommendation to the Licensing Authority, which is the government body that actually grants or denies the product license. Moreover, because the rate of rejection of applications or request for modifications or additional information is very high (99 percent for applications submitted 1987-89), many applications go through an appeals process that may involve additional work on the part of the applicant, reassessment by MCA or CSM, and 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 that 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

[12]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.

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).[13] The most recent data from MCA show that overall approval times are actually somewhat longer than that.[14] 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.

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.[15] 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.

Summary

In sum, the data we have presented show that NDAs are moving more quickly through the drug review and approval process and that the amount of time to obtain an approval is approximately the same in this country and in the United Kingdom. Whether the improvement in FDA time is because of actions that the agency or the pharmaceutical industry has taken or because of some other factors is an issue that was beyond the scope of our study. However, the consistency of all our results supports the conclusion that the reduction in time is real and not an artifact of how

[13]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.

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

[15]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.

time is measured. Further, the magnitude of the reduction (more than 40 percent) and the relative similarity of review times internationally should both be considered in the ongoing discussions of whether it is necessary to change the NDA review process or the agency in order to speed the availability of drugs to patients.

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