Analysis of US Food and Drug Administration Review Intervals for Drugs Approved during the Period 1997–2002

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This research investigates US Food and Drug Administration review intervals in the United States from 1997 through 2002 for three main categories new drugs applications: new drug application (NDA), the supplemental new drug application (SNDAs), and the abbreviated new drug application (ANDA). Review interval for each application was the basis for evaluation and was calculated based on the difference between approval date and the application date. The median review time for all applications was 13.5 months (1.1 years). The median review intervals for ANDAs, NDAs, and SNDAs were 19.1, 12.0, and 10.0 months (1.6, 1.0, and 0.8 years), respectively, during the period. It was found that the median review period for an ANDA was significantly longer than that for an NDA and Snda. Comparison of application class medians revealed significant differences for all 3 pairwise comparisons (all \( P < 0.001 \), Tukey HSD). Within each application category, we compared differences between years. The year effect was not statistically significant for ANDAs or NDAs. NDA median review times were 13.7, 12.0, 12.0, 10.8, 12.5, and 11.7 months (1.14, 1.00, 1.00, 0.90, 1.04, and 0.98 years), while ANDA median review times were 20.4, 19.1, 19.9, 18.6, 18.4, and 21.5 months (1.70, 1.59, 1.66, 1.55, 1.53, and 1.79 years) for 1997, 1998, 1999, 2000, 2001, and 2002, respectively. Year differences were significant for SNDAs \( (P < 0.001) \). The primary source of this difference was a lower median review time during 1997, but there was little difference in median review times for the remaining years.

Keywords: US Food and Drug Administration, drug review time, drug approval, drug development

INTRODUCTION

The US Food and Drug Administration (FDA) review interval for each new application has been an important topic discussed at many levels, including entities such as the United States Congress, major drug manufacturers, numerous consumer groups, some notable economists, and the FDA itself. The review process has been connected with expensive drug research and development (R&D) costs and sharply increasing drug prices in the past 2 decades. In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA). Under the PDUFA, the drug companies agree to pay fees to the FDA and the FDA in turn agrees to time limits on the review process for new applications. The FDA Modernization Act of 1997 authorized additional funds and user fees for the FDA to improve the process of review of human drug applications.

There are several application categories: the new drug application (NDA), the supplemental new drug application (SNDAs), and the abbreviated new drug application (ANDA). Each of these categories is linked to sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act (FFDCA) by the purpose of the drug application. The NDA is the application for a new chemical entity (NCE) that does not yet exist under section 505(b). The SNDAs are mainly for a change that will affect the drug substance and/or drug product of a drug already approved under section 505(b) of the FFDCA. The ANDA pertains to the review and ultimate approval of a generic drug product of an existing drug under section 505(j).

This article reviews the time intervals for three main categories of drug applications that were approved...
from 1997 through 2002. In each of these years, the FDA approved several hundred NDAs. An NDA constitutes the request to allow general marketing of the new drug for prescription use after the sponsor has finished phase 1, phase 2, and phase 3 human clinical test processes (an overview of the FDA drug review process can be found elsewhere).

MATERIALS AND METHODS

FDA drug review times have been explored from many different perspectives. DiMasi\(^3\) conducted a study of approved NCEs. When analyzed by year of approval, the mean approval time decreased from 2.7 years for the period 1990–1993 to 1.7 years for 1994–1995. The average NDA approval time increased during the 1980s but decreased during the 1990s. Novack\(^4\) investigated 19 ophthalmic NDAs and SNDAs approved by the FDA between 1990 and 1996. He found that the median review time decreased from 18 months in 1990 to 10.6 months in 1996. Kaitin and Healy\(^5\) reported their continuous research results for NCE approvals for five 3-year periods. They found that the review time was 35.6, 34.4, 31, 24.4, and 16.8 months (3.0, 2.9, 2.6, 2.0, and 1.4 years) for 1984–1986, 1987–1989, 1990–1992, 1993–1995, and 1996–1998, respectively. Rawson\(^6\) compared the time required for review of new drugs in Canada, Australia, Sweden, the United Kingdom, and the United States during the period 1996–1998. The median review time for the 123 new drugs approved in the United States during this period was 12.3 months (1.0 years). Most of these studies focused on NDAs for new chemical or biologic drugs. Although the research perspectives of these studies were different, 1 common finding was that review time has decreased throughout the 1990s.

Several researchers have recognized the factors that affected the FDA review process and the financial impact on overall drug development. Dranove and Meltzer\(^7\) asked whether important drugs reached the market sooner and developed measures of “time to approval” and “importance” and determined how the latter affected the former. Their analysis led them to assert that more important drugs are developed and approved more rapidly than less important drugs and that the pharmaceutical manufacturers, rather than the FDA, were responsible for the relative acceleration of important drugs.

DiMasi\(^8\) also studied review times from a financial perspective, with the assumption that shorter review times would reduce the total R&D budget. For a representative drug, he estimated that regulatory review time was 18.2 months and discovery/development time was 11.9 years. If the review time could be reduced by 50%, he estimated that average drug development costs (US$802 million) would decrease by 7.6% (US$61 million).

Carpenter\(^9\) tested the political influence on the FDA review time for 450 drugs reviewed from 1977 to 2000. The drug review times appeared insensitive to shifts in the partisanship or ideology of congressional majorities, oversight committees, and presidents. FDA review times were decreasing in (1) the wealth of the richest organization representing the disease treated by the drug, (2) media coverage given to this disease, and (3) a nonlinear function of the number of groups representing a disease. The work by Dranove and Meltzer,\(^7\) DiMasi,\(^8\) and Carpenter\(^9\) investigated relationships influencing drug review times. This study focuses on the statistical analysis of drug review times for the United States from 1997 to 2002. The next section describes the method of data collection.

Data collection

Under the Freedom of Information Act, the FDA publishes approved drug information on its official website. From the published drug information, the date of application, the date of approval, and the category of the drug application was obtained. From 1997 to 2002, the FDA approved about 4170 applications. Submission and approval dates were available for about 80% of these applications on its website before May 2003. This study does not include drug applications not yet approved or drugs that had been approved but not yet published on the FDA website before May 2003.

From the official drug approval letters, the 3 drug application categories (NDA, SNDA, and ANDA) were apparent, although in some instances several applications were approved together under the same drug name. For example, 1 new drug could have several drug applications for different dose forms or there could be different applications for different supplemental purposes for 1 approved drug. Therefore, for this study, every application was treated as an independent case.

The review time for each application was the basis for evaluation. The date that the submission was received was chosen as the application date and the date of the approval letter as the approval date. Review time was then calculated based on the difference between approval date and the application date. If sponsors had withdrawn a submission during review, the resubmission date was chosen as the application date.

Statistical methods

The collected data were statistically analyzed using SPSS software.\(^10\) Because the distribution of the review
interval is skewed to the right, due to the large outliers, the medians (rather than means) of review times of each year and each category were compared, and significance tests conducted on the rank-transformed data. The Tukey honestly significant difference (HSD) was chosen to make post hoc pairwise comparisons as it is one of the more powerful multiple comparison tests. For the purpose of reporting review intervals in months, a “month” was defined as 365.25 days/12 or 30.44 days.

RESULTS

Between 1997 and 2002, the FDA approved about 4170 applications, of which approximately 1700 were ANDAs for generic drugs. From the 4170 applications, we extracted 3421 cases that met the criteria for our study. Among the 3421 cases, 1779 cases were SNDAs, 1164 cases were ANDAs, and 478 cases were NDAs (Fig. 1). The 3421 cases in our study represented about 82% of all approved applications between 1997 and 2002. Among them, the cases of NDAs and SNDAs together represented 91% of total approved NDAs and SNDAs. The ANDAs in our study represented about 68% of all ANDAs approved during the period. Thus, information was available on the FDA website for a greater proportion of NDAs and SNDAs compared with ANDAs.

Trends in NDA and SNDA approvals

NDA and SNDA approvals have increased in recent years. This study contained 62, 78, 82, 96, 69, and 91 NDA cases and 86, 133, 153, 178, 286, and 943 SNDA cases for years 1997, 1998, 1999, 2000, 2001, and 2002, respectively. The number of approved NDAs increased over the period, although not as dramatically as the number of SNDAs, which showed a threefold increase from 2001 to 2002. Figures 2 and 3 display the trends in NDA and SNDA approvals from 1997 to 2002.

Statistical analysis

Application median review times

The median review time for all applications was 13.5 months (1.1 years). The median review intervals for ANDAs, NDAs, and SNDAs were 19.1, 12.0, and 10.0 months (1.6, 1.0, and 0.8 years), respectively, over the period. Figure 4 displays the comparison of median review intervals for ANDAs, NDAs, and SNDAs for the years 1997–2002.

Therefore, the median review time for an ANDA was significantly longer than that for an NDA and SNDA by 7.1 and 9.1 months, respectively. Comparison of application class medians revealed significant differences for all 3 pairwise comparisons (all P < 0.001, Tukey HSD).

Review interval summary statistics

Table 1 shows summary statistics on the review interval by application category and year approved.

Within each application category, we compared differences between years during the 6-year study period. The year effect was not statistically significant for ANDAs or NDAs. Median review time for the NDAs

FIGURE 1. Application category percentages.

FIGURE 2. Approved NDAs have increased from 1997 to 2002.

FIGURE 3. Approved SNDAs increased each year and showed a threefold increase from 2001 to 2002.

(most of the applications were for NCEs) was 13.7, 12.0, 12.0, 10.8, 12.5, and 11.7 months (1.14, 1.00, 1.00, 0.90, 1.04, and 0.98 year), while median review time for ANDAs was 20.4, 19.1, 19.9, 18.6, 18.4, and 21.5 months (1.70, 1.59, 1.66, 1.55, 1.53, and 1.79 year) for 1997, 1998, 1999, 2000, 2001, and 2002, respectively. Figure 5 displays the comparison of median review intervals for NDAs, and Figure 6 displays the comparison of median review intervals for ANDAs for the years 1997–2002.

However, year differences were significant for SNDAs ($P < 0.001$). The primary source of this difference was a lower median review time during 1997, but there was little difference in median review times for the remaining years. Figure 7 shows the distribution of review times over the period for each application category in a box plot.

**DISCUSSION**

It has been documented that FDA review times decreased throughout the 1980s and into the 1990s. The FDA itself attributes the shorter turnaround time during the first half of the 1990s to expansion of the agency’s resources and higher quality submissions from the pharmaceutical industry. It specifically points to the PDUFA created in 1992 as the driving force for the decreased review times from 1993 to 1998. However, there has been some conjecture regarding the trend of drug review times at the FDA recently. A number of authors cite evidence of the drug review process taking longer. These authors attribute the longer review times to a number of issues including increased numbers of drug applications and concerns over drug safety. On the other hand, some cite that the FDA is just showing more caution since there has been a number of cases in which approved drugs were pulled off the market.

This research has illustrated that when controlled for application type and year, the differences in the median review time from 1997 to 2002 for ANDAs and NDAs are not significantly different. This finding is contrary to the notion that review intervals have decreased over the past 6 years. However, it can be shown that the median review times for SNDAs are significantly different during the period 1997–2002. This result is somewhat spurious. From the summary statistics and box plot, it is apparent that the review interval for 1997 is lower, but there was little difference in median review time for the remaining years.

In turn, when controlling just for application type, the median review time of the ANDAs for review of a generic drug during 1997–2002 was 19.1 months and is
Table 1. Review interval summary statistics by application category within year approved

<table>
<thead>
<tr>
<th>Year approved</th>
<th>Category</th>
<th>No. of cases</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Median</th>
<th>Mean</th>
<th>Review time SD</th>
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<td>62</td>
<td>1.02</td>
<td>57.79</td>
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<td>225</td>
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<tr>
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</table>

If an approval date was the same day as the submission date, the value of the review interval would be zero.

FIGURE 5. NDA median review times in months for 1997–2002.
significantly different from that of an NDA and SNDA (12.0 and 10.0 months, respectively). One of the possible explanations for these differences might come from the different review policies and resources for new and the generic drugs. For example, the FDA will give an accelerated review to some new drugs for serious and life-threatening illnesses for which satisfactory treatments are lacking. This allows an NDA to be approved before measures of effectiveness of the new drug are available. One of the other possible explanations might come from the larger numbers of ANDAs each year. The FDA had to allocate more resources to process the large number of ANDAs.

The different review policies for new drug and generic drugs may push new drugs to the market faster than the generic drugs. The FDA faces a balance between allocating resources between new drug reviews and the generic drug review process. If more resources go to the new drugs, the new drugs can go to the market faster and those patients who suffer from unsuccessfully treated diseases can benefit from the newly available medicine. The faster new drug review process also can encourage new drug R&D, especially for pharmaceutical companies whose strategy focuses on new drug development. Conversely, if more resources are allocated to the generic drug review

NDAs during the 6 years are not significant. The median review time for SNDA during 1997 is lower, but there was little difference in median review time for the remaining years.
process, the review time of generic drugs can be reduced and generic drugs can go to market earlier. From the market and economic perspective, competition brings down the price of a product or service; therefore, more drugs making it to the consumer in a more timely fashion should bolster competition, resulting in lower drug prices.

In all, this study found that the median review time for the period 1997–2002 and covering all drug categories was 13.5 months (1.1 year). When each unique drug category is examined, it can be shown that, in the case of ANDAs and NDAs, there has been no significant change in drug review times during the 6 years reviewed by this study. However, for SNDAs, the median review time increased from 6.2 months in 1997 to 10.0 months in 1998 and then remained relatively constant thereafter. It appears that the pharmaceutical industry, the FDA itself, and the general public all want faster drug review times. These pressures, along with the increased numbers of new applications each year and the current 1.1-year median review benchmark time, suggest that the FDA has an interesting job ahead to effectively use their resources to maintain and improve the relatively stable review times of the past 5 years while balancing the issue of safety.

REFERENCES