

**Department of Health and Human Services**

**OFFICE OF  
INSPECTOR GENERAL**

**FDA's Review Process  
for New Drug Applications**

**A Management Review**



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# EXECUTIVE SUMMARY

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## PURPOSE

To assess how well the Food and Drug Administration manages its new drug application review process.

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## BACKGROUND

The Food and Drug Administration (FDA) receives new drug applications (NDAs) from sponsors, typically pharmaceutical companies, and reviews these applications for scientific evidence pertaining to the safety and efficacy of drugs. Based on its assessments, the FDA determines whether drugs can be marketed in the United States.

The Prescription Drug User Fee Act (PDUFA), enacted in 1992, authorized FDA to collect user fees from sponsors to help speed up the review of NDAs. It also established time goals for FDA's reviews. In 1997, the FDA Modernization Act reauthorized user fees for another 5 years. It shortened the time goals and called for FDA to work more collaboratively with sponsors. In June 2002, the Public Health Security and Bioterrorism Preparedness Act of 2002 once again reauthorized user fees. The part of this Act addressing user fees is referred to as PDUFA III.

This inquiry focuses on FDA's Center for Drug Evaluation and Research (CDER), which reviews NDAs. This inquiry does not assess the scientific merit of the decisions that FDA has made. Instead, it examines how well FDA carries out its NDA review process. This report draws heavily on the opinions of CDER officials. We surveyed CDER reviewers, receiving an estimated 47 percent response rate (N=401) and interviewed about 80 CDER officials, including managers. In addition, we surveyed sponsors, receiving a 60 percent response rate (N=72), reviewed files for all 15 new molecular entities approved by CDER in fiscal year (FY) 2001, analyzed CDER data regarding the number of advisory committees, observed 17 CDER meetings, interviewed 20 stakeholders, and reviewed relevant FDA policies and procedures. We also drew on data from an internal survey conducted by CDER of a random sample of 188 reviewers that had a 72 percent response rate.

We conducted this inquiry prior to the implementation of PDUFA III. Where appropriate, we indicate the potential impact of PDUFA III on our findings.

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## FINDINGS

### **FDA's new drug application review process has several strengths that contribute significantly to its effectiveness.**

**Both FDA reviewers and sponsors have confidence in the decisions FDA makes.** Our review underscored that FDA's NDA review process is science-based and comprehensive. This is supported by the comments of both FDA reviewers and sponsors. Seventy-eight percent of FDA respondents and 86 percent of sponsors indicated in our surveys that they were confident in the decisions FDA makes with regard to a drug's efficacy.

**FDA is highly responsive to the time goals required under the Prescription Drug User Fee Act and the FDA Modernization Act.** In 1993, median total approval time for CDER was 27 months for standard NDAs classified as new molecular entities; in 2001, it was 19 months. The reduction in approval times helps to ensure timely access to new medications that can benefit the public health.

**FDA works collaboratively with sponsors.** In FY 2001, CDER conducted 1,021 formal meetings with sponsors. In these meetings, FDA provides valuable advice to sponsors that can help speed up the drug development process.

**FDA has taken numerous steps to improve efficiency and consistency.** In 2000, CDER issued about 40 guidance documents, most of which it directed to sponsors. Between 1996 and 2001, CDER issued about 140 policies to help guide reviewers. It also now accepts applications electronically.

**FDA relies on expert scientific reviewers.** Both sponsors and reviewers agreed that FDA's in-house expertise is a key asset of the review process. Funds from user fees have allowed FDA to increase the number of employees for drug reviews by about 700 employees over the past 10 years.

### **But workload pressures increasingly challenge the effectiveness of the review process.**

Reviewers are under constant pressure to meet time goals. They not only review NDAs, but also other key documents submitted by sponsors, some of which also have time goals attached. At the same time, reviewers must provide advice to sponsors and stay abreast of the latest scientific advances in their fields. Below, we present the consequences of these workload pressures.

**Reviewer concerns about time pressures.** Forty percent of FDA survey respondents who had been at FDA at least 5 years indicated that the review process had worsened during their tenure in terms of allowing for in-depth, science-based reviews. Respondents cited lack of time as the main reason. According to 58 percent of FDA respondents, the allotted 6 months for a priority review is inadequate. This is considerably higher than the 25 percent of respondents who indicated that the allotted 10 months for a standard review is inadequate.

Reviewer concerns about time constraints do not necessarily mean that there is a threat to public health. We have no evidence of a public health concern nor did we seek to obtain such evidence. Reviewers commented in interviews that they did not believe that they were ignoring key information or data contained in the applications in order to meet time goals. The FDA has also received the 4th highest composite score out of the 13 operating divisions within the Department of Health and Human Services on the 2002 Secretary's Quality of Work Life Survey on Organizational Climate, which indicates a positive work environment. However, our survey data do indicate a significant management issue warranting attention.

The PDUFA III should help to address reviewers' concerns about time pressures, as CDER estimates hiring close to 300 additional employees over the next 5 years with funds from user fees.

**Less use of advisory committees.** Advisory committees are comprised of independent scientific experts who provide advice to FDA during the review process. The number of advisory committee meetings CDER held for NDAs decreased from 40 in 1998 to 23 in 2001. Although the declining number of NDAs submitted by sponsors has contributed in part to this decline, FDA managers also pointed out that they have little time to hold these meetings.

**Insufficient time for raising scientific disputes.** Pressure to meet time goals may inhibit the raising of disputes. Reviewers may be reluctant to raise disputes due to concerns about slowing down the process. Twenty-one percent of FDA respondents indicated that the work environment allowed for the expression of differing scientific opinions to a small or no extent.

**Contributing to staff turnover.** The FDA data show that medical officers and pharmacologists had the highest attrition rates within CDER for FY 2001, 8.4 percent and 6.9 percent respectively, compared to the overall rate of 5.5 percent. On an internal CDER survey, 50 percent of reviewers who responded indicated that their workloads are influential reasons to consider leaving FDA.

**Less time for reviewers to participate in professional development and to conduct research to improve drug development.** The FDA has policies and programs in place to encourage professional development, yet 59 percent of FDA respondents indicated that they have little time to participate in professional development activities. Similarly, reviewers have little time to conduct research on drug development using the clinical trial databases FDA has obtained from sponsors.

### **Several factors have contributed to the workload pressures.**

Time goals have been beneficial, but at the same time they have created pressure on reviewers to work quickly. The FDA has little flexibility in reassigning staff to handle increased workloads. The FDA's dual roles as advisor and reviewer demand substantial time and resources; the CDER held over 1,000 meetings with sponsors in FY 2001. Incomplete and disorganized applications can cause delays. The 15 new molecular entities we reviewed contained, on average, 38 amendments to the original application. Inefficiencies in the process also contribute to workload pressures.

As we have already indicated, PDUFA III will provide FDA additional resources to hire more staff that should help address these workload pressures. It also calls for FDA to conduct several studies aimed at improving the efficiency of the process.

### **Other factors also challenge the effectiveness of the review process.**

**Rush to finalize drug labels at the end of the process.** Although labeling negotiations must occur toward the end of the process, we found that negotiations were considerably compressed. Eighty-two percent of FDA respondents indicated that labeling negotiations contribute to delays. Twenty-seven percent of labeling amendments for the 15 new molecular entities we reviewed were submitted in the last 14 days of the review process. The rush to finalize labels at the end of the review process can be caused by the lengthy discussions that often occur between FDA and the sponsor regarding the information to include on the label. The FDA has numerous activities underway to help address this issue.

**Reviewers' uncertainty about postmarketing commitments.** Postmarketing commitments are made by the sponsor at the time of approval and can include additional studies to further define the safety and effectiveness of the drug. Reviewers indicated that they were often uncertain about what types of postmarketing commitments to request of sponsors. The PDUFA III calls for FDA to issue several guidance documents regarding risk management after the drug is approved. These documents should help to clarify the use of postmarketing commitments.

**Limited public disclosure of FDA’s rationale for decisions.** We reviewed the information on CDER’s website for 15 new molecular entities, and in no case did FDA provide a summary document that explained the overall basis for approval. The FDA does not routinely provide summary information for approved drugs, nor is it required to do so. We found it took 7.6 months, on average, for FDA to post the technical information it does disclose on its website after a drug is approved. For drugs that FDA reviewed but did not approve, FDA disclosed almost no information regarding the basis for its decisions. The FDA’s regulations limit such disclosure.

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## **CONCLUSION**

**FDA’s NDA review process has several strengths. However, reviewers face workload pressures that increasingly challenge the effectiveness of the process.**

Beyond these pressures, three other factors threaten the effectiveness of the process: the rushed review of drug labels that takes place toward the end of the review process, the limited guidance available to reviewers in determining the extent and type of postmarketing commitments to request of sponsors, and the limited information that FDA makes available to the public on the basis for its decisions concerning NDAs. Overall, these findings present a significant warning signal, one, that if not fully addressed, could jeopardize the gains that FDA has made in recent years.

**The enactment of PDUFA III presents significant opportunities to address many of the findings in this report.**

We recognize that FDA has already identified many of the concerns presented in this report and has numerous efforts underway to address them. In particular, the enactment of PDUFA III, which FDA played a critical role in developing with sponsors, presents significant opportunities to address many of our findings. It calls for an increase in user fees that CDER estimates will allow it to hire close to 300 additional employees over the next 5 years. Over time, this could help considerably in relieving the workload pressures that we have emphasized. In addition to resources, PDUFA III calls for FDA to conduct several activities aimed at improving the process. These activities will help to address many of the findings in this report, including efficiency, labeling negotiations, and the use of advisory committees. In addition, PDUFA III calls for significant attention to be placed on postmarketing commitments. For the first time, funds from user fees can be used to monitor drugs after they are on the market. It also calls for FDA to develop several guidance documents on risk management.

Our first recommendation offers additional steps that FDA can take as it implements PDUFA III to ensure that it takes full advantage of these opportunities to address our

findings. We also make four other recommendations to FDA to improve the NDA review process that are not addressed in PDUFA III. We direct all our recommendations to CDER.

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## RECOMMENDATIONS

### 1. Take full advantage of the opportunities in PDUFA III.

- ▶ Conduct a retrospective examination of recent NDA reviews to determine the capacity of reviewers to conduct in-depth, science-based reviews.
- ▶ Evaluate the adequacy of current staffing levels and the workload distribution among the 15 review divisions within CDER, and implement a system that in real time would indicate the status of an NDA and the time spent in reviewing its specific parts.
- ▶ Assess how amendments to the original application, internal processing delays, and labeling negotiations affect FDA's capacity to make timely, first-cycle review decisions.
- ▶ Offer further guidance on the best way to handle scientific disputes that occur among reviewers, and how to balance the role of reviewing NDAs and the role of advising sponsors throughout the drug development process.
- ▶ Include case studies of past reviews as part of training programs for reviewers to illustrate good review principles and foster consistency among divisions.
- ▶ Provide a list of the various postmarketing commitments that FDA reviewers can request of sponsors and suggestions for when each could be considered.

### 2. Determine whether the significant workload pressures discussed in this report justify any exceptions to the current time goals regarding new drug applications to allow for more in-depth reviews.

As we have indicated, the Prescription Drug User Fee Act and the FDA Modernization Act have been positive forces for the review process. However, it is important that an appropriate balance exists between timeliness and the ability to conduct a comprehensive review. Our data show that reviewers face significant workload pressures. Therefore, FDA could examine if it would be beneficial to extend the review clock by 1 or 2 months when it chooses to use an advisory committee and to consider modifying the current 10-month time goal for standard NDAs by 1 or 2 months.

### 3. Reject applications that are incomplete and of poor quality that can create delays in the new drug application review process.



A timely review process depends not only on FDA, but also on sponsors submitting complete and well organized NDAs. Toward that end, FDA could reexamine its policies for refusal-to-file and its guidance to sponsors on the content and format of applications to ensure that they make explicit FDA's requirements.

#### **4. Provide the public with a clear and timely explanation of decisions on new drug applications.**

The FDA could provide on its website a succinct explanation of its rationale for approving an NDA. It could also provide the same explanation when it decides not to approve an NDA. Disclosing such information could help convey to the public the independent role that FDA plays in the review process and that FDA does not approve all drugs. Further, this could help sponsors gain a better understanding of the criteria FDA uses in its review process and could lead to improved NDAs in the future.

#### **5. Conduct or support research that takes greater advantage of its vast clinical trial databases to identify ways to improve drug development.**

The results of this research, over time, could be highly cost-effective, contributing to better clinical trial designs and more efficient drug development.

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### **AGENCY COMMENTS**

The FDA reviewed a draft of this report, and overall, it concurred with our conclusions and recommendations. In its comments, FDA outlined numerous activities it has underway or planned to address our recommendations. Specifically, FDA indicated that it is reviewing its workload distribution and has studies underway to examine delays in the review process. The full text of FDA's comments can be found in Appendix A.

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# INTRODUCTION

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## PURPOSE

To assess how well the Food and Drug Administration manages its new drug application review process.

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## BACKGROUND

The Food, Drug, and Cosmetic Act requires the Food and Drug Administration (FDA) to review and approve all new drugs before they can be marketed in the United States. The FDA evaluates new drugs based upon the scientific evidence obtained from clinical studies and other research conducted by a drug's sponsor, typically a pharmaceutical company. Sponsors submit this information to FDA in a new drug application (NDA). Based on its review of the application, FDA assesses the safety and efficacy of the drug and determines whether it can be marketed in the United States. (We provide a primer that gives an overview of the review process on page 5. Appendix B contains a glossary of key terms.)

### **The Prescription Drug User Fee Act and the Food and Drug Administration Modernization Act**

In response to the public's demand for greater access to new drugs to treat life-threatening illnesses, the 1992 Prescription Drug User Fee Act, referred to as PDUFA I, was enacted. The main purpose of PDUFA I was to reduce the time it takes FDA to review new drugs for market approval. It authorized FDA to collect user fees from sponsors to be used towards speeding up the NDA review process. It also established time goals for FDA's review of NDAs. The FDA reports annually to Congress on how well it has met these time goals (see Appendix C for a list of the goals).

In 1997, user fees were reauthorized as part of the Food and Drug Administration Modernization Act. The section of the Act that addresses user fees, referred to as PDUFA II, tightened the deadlines in the goals. It also added new provisions to help speed up the entire drug development process. Most notably, it required FDA to meet with sponsors upon request and codified many existing FDA policies intended to bring life-saving treatments to market faster.

User fees have provided additional resources for FDA. The FDA's Center for Drug Evaluation and Research (CDER) total costs in fiscal year (FY) 2000 for reviewing NDAs was \$187 million, of which \$86 million was paid for by user fees. The FDA primarily used the funds from user fees to hire more staff and to implement computer systems to speed up its review of NDAs.

### **Prescription Drug User Fee Act III**

The PDUFA II expired on September 30, 2002. In June 2002, user fees were once again reauthorized, referred to as PDUFA III, as part of the Public Health Security and Bioterrorism Preparedness Act of 2002. The PDUFA III establishes time goals and outlines activities FDA will conduct over the next 5 years using the funds from user fees (see Appendix D).<sup>1</sup> The PDUFA III went into effect on October 1, 2002.

Most notably, PDUFA III increases user fees to help provide FDA with additional resources. According to a press release from the U.S. Department of Health and Human Services, "the law puts PDUFA III on sound financial basis."<sup>2</sup> In FY 2002, FDA, including both the Center for Biologics Evaluation and Research and CDER, estimates it collected about \$160 million from user fees. Under PDUFA III, total funds from user fees should reach \$223 million in FY 2003, and gradually increase over the next 5 years to reach \$260 million in FY 2007. With increased resources, CDER estimates it will hire close to 300 additional employees over the next 5 years.

### **Concerns about the adequacy of FDA's review process**

Critics allege that, in the rush to meet its time goals, FDA fails to identify key risks associated with drugs. Critics also raise concerns that FDA works too closely with pharmaceutical companies, lacks independence, has lowered its review standards, and conducts inadequate monitoring of drugs already on the market. Critics point to the recent drug withdrawals as evidence of their concerns. Between 1997 and 2001, sponsors voluntarily withdrew 13 drugs due to safety concerns. Five of them were approved prior to PDUFA, and one has since returned to the market. New molecular entities (NMEs) are drugs containing an active ingredient that has never been approved for marketing in the United States. According to CDER's analysis, the rate of safety-based withdrawals for NMEs has remained relatively constant for periods prior to and after the enactment of the Prescription Drug User Fee Act in 1992. According to CDER's analysis, between FY 1983 and FY 1992, the rate of safety-based withdrawals for NMEs, based on the year of receipt, was 2.5 percent, and between FY 1993 and FY 2002, it was 2.8 percent (see Appendix E for additional analysis). The FDA's own review of many of these withdrawals concluded that they were not attributable to faster review times.<sup>3</sup>

## Our Inquiry

Our inquiry focuses on CDER, one of two Centers within FDA that reviews NDAs. We did not evaluate the Center for Biologics Evaluation and Research's process for reviewing NDAs. Our inquiry focuses on how well CDER carries out its NDA review process. We did not examine the scientific merit of FDA's decisions. We conducted this inquiry at the request of the director of CDER and prior to the implementation of PDUFA III. Where appropriate, we indicate the potential impact of PDUFA III on our findings. We also highlight activities FDA has underway to address our findings.

We use the term "FDA reviewers," broadly, unless otherwise specified, to refer to CDER officials involved in the NDA review process. This includes office directors, division directors, primary reviewers, secondary reviewers, and project managers within the Office of New Drugs, the Office of Pharmacoeconomics and Statistical Science, the Office of Pharmaceutical Science, and the Office of Medical Policy.

## Methodology

This inquiry is based on multiple data sources (see Appendix F). This inquiry draws heavily on a web-based survey of all CDER primary reviewers, secondary reviewers, and division directors. We received 401 responses for an estimated response rate of 47 percent. We conducted a mail survey of all 119 sponsors, excluding one federal agency, that had at least one NDA approved by CDER in the years 1999, 2000, or 2001. We received 72 responses from sponsors, resulting in a 60 percent response rate. We also drew on data from an internal survey conducted by CDER of a random sample of 188 reviewers that had a 72 percent response rate.

We conducted a file review of all new molecular entities that CDER approved in FY 2001 (N=15). For these 15 drugs, we analyzed CDER's receipt dates for all amendments submitted to the application. We analyzed CDER's data on advisory committees. We observed 17 CDER meetings that occurred throughout the drug development process, including internal meetings and meetings between CDER officials and sponsors. We also reviewed relevant FDA laws, regulations, policies, and procedures.

To enhance our understanding, we conducted numerous interviews. We interviewed CDER officials, including 17 office directors, 27 division directors, and 18 primary and secondary reviewers of NDAs, including project managers. We conducted 9 interviews with representatives from pharmaceutical companies and 15 interviews with other stakeholders, such as consumer advocates, patient advocates, and scientific experts.

We conducted this inspection in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

# PRIMER ON FDA'S NDA REVIEW PROCESS

This primer refers to the review of NDAs conducted by CDER.

**Review Clock.** The review clock is the time between FDA's receipt of the application and FDA's decision. The PDUFA II calls for FDA in FY 2002 to review and act upon 90 percent of standard NDAs within 10 months and 90 percent of priority applications within 6 months. *Priority* applications are for drugs that are a significant improvement over drugs already on the market to treat the same condition. *Standard* applications are applications not classified as priority.

**Contents of a New Drug Application.** A sponsor, typically a pharmaceutical company, submits the NDA to FDA to obtain marketing approval for a drug within the U.S. The application contains data regarding the safety and efficacy of the drug that the sponsor obtained during its research and development. These data include the results of clinical trials, pharmacology and toxicology data, chemistry and manufacturing data, and proposed packaging and labeling information.

**Filing Review.** When FDA receives an application, the review clock begins. The FDA assigns the application to the appropriate therapeutic review division, of which there are 15. The FDA has 60 days, from the receipt of the application, to determine whether it is adequate for review. If the application is deemed inadequate or incomplete, FDA can refuse to file it and the sponsor can resubmit it later. If the application is complete, FDA notifies the sponsor that the application has been filed.

**Reviews within Individual Disciplines.** After the application is filed, FDA assigns the application to a team of multi-disciplinary reviewers. These reviewers are referred to as primary reviewers. They represent a variety of scientific disciplines, including medicine, pharmacology, statistics, and chemistry. The FDA also assigns a project manager that facilitates the review process and serves as a liaison between FDA and the sponsor. The reviewers, except for the project manager, evaluate the information in the application relevant to their areas. If necessary, the primary reviewer can request additional information from the sponsor. Based on the review, the primary reviewer may make a recommendation on the action FDA should take with respect to the drug. The primary reviewer's work is checked by a secondary reviewer within the same discipline.

**Advisory Committees.** The FDA may convene an advisory committee to assist with the review of an application. The committee comprises scientific experts from outside FDA and may also have consumer, patient, and industry representatives. The committee conducts its own review of the application, usually in a public forum, and advises FDA on scientific issues related to the application. It also votes on the action FDA should take with respect to the drug. The committee's recommendations are not binding on FDA.

**Communication with Sponsors.** Throughout the process, FDA and the sponsor communicate through in-person meetings, telephone conferences, letters, e-mails, and faxes. Communication allows sponsors and FDA to seek clarification, when necessary.

**Labeling Negotiations.** Toward the end of the review process, FDA and the sponsor negotiate the drug's final package label. Each element of the label requires FDA approval, including the indications, dosing, directions for use, and safety information.

**Inspections of Manufacturing and Clinical Sites.** The FDA inspects the manufacturing facilities for the drug. It may also inspect a sample of clinical trial locations to verify the accuracy of the data contained within the application.

**Decision.** Once all the reviews are complete, the division director and/or the office director evaluate the reviews and make FDA's decision. Five office directors oversee the 15 review divisions. The FDA can take three actions: (1) approval – the drug can be marketed in the U.S., (2) approvable – problems exist with the application that need to be addressed before the drug may be approved, and (3) non-approvable – the application has more significant problems that may require additional research on the drug and may require reformulation of the drug product. The review clock ends once FDA makes its decision and issues a letter to the sponsor.

**Review Cycles.** The first-review cycle begins when FDA receives the application and ends when FDA makes its decision. Multiple review cycles occur when an application receives an approvable or non-approvable decision from FDA, and the sponsor revises the application and resubmits it to FDA, starting another cycle. When the sponsor resubmits the application, the review clock restarts and FDA receives either 2 or 6 months to review the revised application, depending on the information in the resubmission.

**Total Approval Time.** Total approval time is from FDA's receipt of the original application to the application's approval. This time can include multiple review cycles and the time spent by the sponsor revising the application between review cycles.

# FINDINGS

Our review of FDA's NDA review process disclosed that it has several strengths that contribute significantly to its effectiveness. Both reviewers and sponsors have confidence in the decisions FDA makes. Review times have dropped considerably. FDA works more collaboratively with sponsors, and it has taken several steps to enhance efficiency and consistency. But we also found that workload pressures increasingly challenge its effectiveness.

Our review included: (1) a survey of CDER reviewers resulting in 401 responses for an estimated 47 percent response rate, (2) interviews with over 100 CDER officials and stakeholders, including industry representatives, (3) a survey of sponsors resulting in 72 responses for a 60 percent response rate, and (4) a detailed document review of all 15 new molecular entities approved drugs in FY 2001.

Although reviewers have confidence in the decisions FDA makes, 40 percent of FDA survey respondents who had been at FDA at least 5 years indicated that the review process had worsened during their tenure in terms of allowing for in-depth, science-based reviews. Respondents cited lack of time as the main reason. Reviewer concerns about time goals do not mean there is a threat to public health, but they do indicate a significant management issue warranting attention. This pressure to meet time goals may also inhibit the raising of disputes as reviewers may be reluctant to raise them due to concerns about slowing down the process. Twenty-one percent of FDA respondents indicated that the work environment allowed for the expression of differing scientific opinions to a small or no extent.

In addition to workload pressures, other factors challenge the effectiveness of the process. These other factors include the rush to finalize drug labels at the end of the review process, reviewers' uncertainty about the types of postmarketing commitments to request of sponsors, and limited public disclosure.

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## **FDA's new drug application review process has several strengths that contribute significantly to its effectiveness.**

### **Reviewers and sponsors have confidence in the decisions FDA makes.**

Our observations, a review of FDA documents, and extensive interviews with FDA reviewers and stakeholders underscored that FDA's NDA review process is science-based and comprehensive. This is supported by the comments of FDA reviewers and sponsors. Seventy-eight percent of FDA respondents and 86 percent of sponsors indicated in our surveys that they were confident in the decisions FDA makes with regard to a drug's



efficacy. And 64 percent and 82 percent, respectively, were confident in FDA's decisions regarding the safety of a drug.

### **FDA is highly responsive to the time goals required in the Prescription Drug User Fee Act and the FDA Modernization Act.**

The CDER met all but 2 of its 20 time goals in FY 2000 (see Appendix C). In meeting these goals, it reduced its total approval time for NDAs. In 1993, median total approval time for CDER was 27 months for standard NDAs classified as new molecular entities; in 2001 it was 19 months. The reduction in approval times helps to ensure timely access to new medications that can benefit public health. Furthermore, the overall time to develop and market a new drug has decreased in part due to FDA's assistance. In the early 1990s, drugs classified as new molecular entities took an average of 7 years to go from clinical testing to the marketplace; by 1998, the elapsed time dropped to a little over 5 years.<sup>4</sup>

### **FDA is highly responsive to the mandate in the Food and Drug Administration Modernization Act to work collaboratively with sponsors to expedite the drug review process.**

The FDA Modernization Act requires FDA to hold formal meetings with sponsors upon request. FDA has devoted substantial resources to meet this requirement; in FY 2001, CDER conducted 1,021 formal meetings with sponsors. In these meetings, most of which occur prior to the NDA review process, FDA provides valuable advice to sponsors. The FDA's advice can play an important public health role by helping to facilitate efficient and high quality drug development.

Formal meetings held prior to and during the clinical testing of drugs allow FDA to address problems early in the drug development process. Both FDA reviewers and sponsors identified early interaction as a strength of the process. According to 94 percent of FDA respondents and 96 percent of sponsors responding to our surveys, interaction between sponsors and reviewers during this stage contributed to an effective NDA review process. For example, in one meeting we observed that FDA encouraged additional toxicity testing of all human subjects in the clinical trial when the sponsor proposed testing just a sample of the subjects. In another meeting, FDA suggested, based on preliminary data, that the sponsor focus more carefully on safety issues as the research progressed. And in several meetings, FDA stressed the importance of statistical rigor and of developing a clinical trial design that anticipates how the product will be used in clinical practice.

The FDA and sponsors also meet and discuss issues relating to the content and format of an NDA immediately prior to and during the review process. The purpose of this

collaborative approach is to produce higher quality NDAs and more efficient reviews. Ninety-eight percent of sponsors and 89 percent of FDA respondents reported in our surveys that interaction during the NDA review process contributed to an effective review process.

### **FDA gives considerable attention to synthesizing information across review disciplines.**

The FDA relies on multi-disciplinary teams to review NDAs. These teams meet throughout the review process to discuss the status of their reviews and to share ideas. We observed several of these internal meetings and found that the review teams addressed key issues, such as additional information to request from sponsors, unresolved safety concerns, labeling issues, and postmarketing commitments.

Seventy-four percent of FDA respondents to our survey indicated that the NDA review process adequately integrates information across review disciplines. Time goals have provided an incentive for review team members to work on the same application at the same time. In the past, review team members tended to review the application sequentially. Now, more dialogue occurs among review team members throughout the process. Medical officers and statistical reviewers work particularly close and sometimes write a joint evaluation. The FDA also locates members of a review team close to one another to encourage more interaction.

### **FDA has taken several steps to help foster efficiency and consistency in the process.**

With the funds from user fees, FDA implemented a computer infrastructure that allows it to receive NDAs electronically. CDER began accepting NDAs electronically in 1999. Currently, about 70 percent of NDAs have some electronic component and one-third are completely electronic. Reviewers can now use computer programs to conduct their own analysis of databases submitted by sponsors instead of requesting an analysis from sponsors, which can lead to delays. Reviewers can also conduct quick searches for key words or phrases in an electronic document instead of sifting through hundreds of pages by hand. This is particularly helpful when reviewing thousands of individual patient records.

To help foster consistency, FDA has issued numerous guidance documents and internal policies. In 2000 alone, CDER issued about 40 guidance documents, mostly directed toward industry. Since 1996, it issued about 140 policies to guide reviewers covering a wide range of topics. Although some reviewers are concerned that guidance documents and policies are too rigid, FDA's aim is to ensure that minimum standards are met and

key issues are addressed. For example, CDER recently issued a policy requiring reviewers to use discipline-specific templates for their written evaluation of NDAs. These templates help to ensure that reviewers address key issues in the course of their evaluation and present them in a standard format. Sixty-nine percent of FDA survey respondents who had used the templates indicated that they were helpful.

### **FDA relies on a core of expert scientific reviewers.**

The FDA's in-house expertise is a key asset of the review process. The FDA is comprised of hundreds of scientific experts, including physicians, chemists, statisticians, pharmacologists, and toxicologists, most of whom have advanced degrees. Reviewers bring scientific and technical expertise and a strong commitment to public health. Many have left positions in academia and private industry to work at FDA and serve the public. With funds from user fees, FDA has expanded its cadre of reviewers. By the year 2002, CDER will have hired about 700 additional employees using funds from user fees, in addition to the 750 funded through appropriations.

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### **But workload pressures increasingly challenge the effectiveness of the new drug application review process.**

Reviewers work under the constant pressure of the review clock. They not only review NDAs, but also conduct other types of review activities, some of which also have time goals attached. They must provide advice to sponsors throughout the drug development process and stay abreast of the latest scientific advances in their field, both of which contribute to the demands of the job. The importance of FDA's decisions also adds to the pressure, as these decisions have serious consequences for public safety. In this section, we address the consequences of these workload pressures. In the next section, we address the causes of these pressures.

### **Reviewer concerns about time pressures.**

An effective review process not only examines the information submitted by the sponsor, but also asks what, if any, additional information should have been submitted. For example, have all the reasonable safety considerations been explored, and should any additional studies be conducted to adequately address safety and efficacy? In raising these questions, reviewers must draw upon the experiences of FDA and their own scientific and regulatory knowledge.

Yet, in this fast-paced environment, reviewers sometimes find it difficult to conduct reviews that are as in-depth as they would like. Forty percent of FDA respondents who

had been at FDA at least 5 years indicated that the review process had gotten worse in terms of allowing sufficient time for in-depth, science-based reviews. Reviewers are particularly concerned with priority reviews. According to 58 percent of FDA respondents, the allotted 6 months for a priority review is inadequate. This is considerably higher than the 25 percent of respondents who indicated that the allotted 10 months for a standard review is inadequate.

Reviewer concerns about time do not necessarily mean that there is a threat to public health. We have no evidence of a public health concern nor did we seek such information. But, these concerns do indicate a significant management issue warranting attention.

Despite these concerns, reviewers were confident that FDA's final decisions regarding NDAs are appropriate. Seventy-eight percent of FDA respondents to our survey were confident in the efficacy decisions FDA makes. Although reviewers commented in interviews that time pressures have made their jobs more difficult, they did not believe that they were ignoring key information or data contained in NDAs in order to meet time goals. It is also important to acknowledge that FDA received the 4th highest composite score out of the 13 operating divisions within the Department of Health and Human Services on the 2002 Secretary's Quality of Work Life Survey on Organizational Climate, which indicates a positive work environment. The CDER's composite score was also high compared to the overall Department.

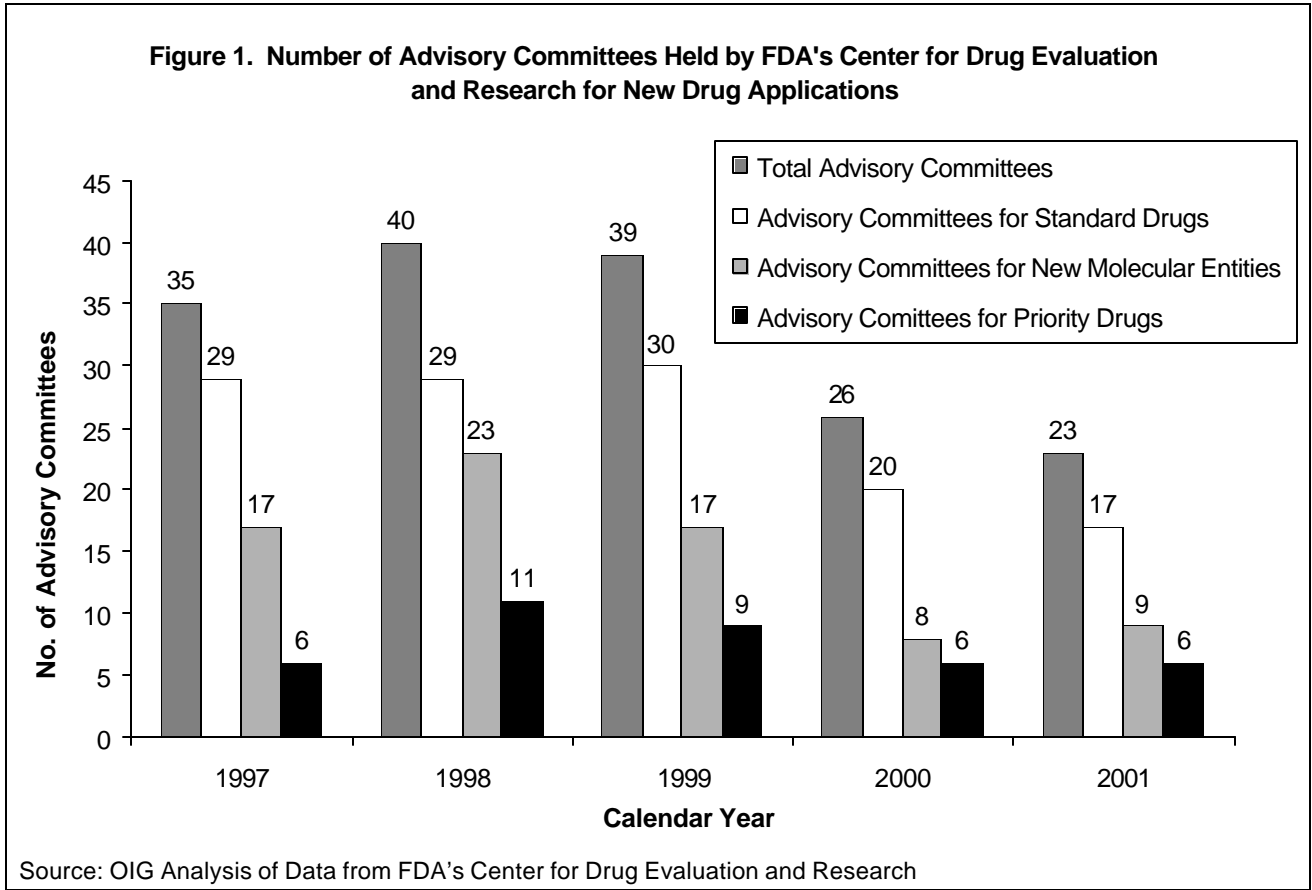
The PDUFA III acknowledges the workload pressures that reviewers face and calls for FDA to receive more resources. With these additional resources, CDER estimates that it will hire close to 300 additional employees over the next 5 years. This will help to alleviate some of the workload pressures.

### **Workload pressures may contribute to less use of advisory committees.**

Advisory committees provide valuable advice to FDA on NDAs. These committees consist of independent scientists, researchers, industry representatives, and consumer and patient advocates. In our surveys, 78 percent of FDA respondents and 81 percent of sponsors indicated that advisory committees were helpful in providing independent advice to the FDA. The majority of advisory committees are open to the public and provide an important opportunity for public discussion and involvement.

However, there is little time to hold these meetings and still meet the time goals. Our analysis of data from CDER shows less use of advisory committees in recent years. The number of advisory committee meetings associated with an NDA decreased from 40 in 1998 to 23 in 2001 (see Figure 1 on the following page). In part, this decrease may be

due to a reduction in the number of NDAs that sponsors have submitted in recent years. The number of NDAs, including both priority and standard, filed by CDER has dropped from 124 in 1997 to 97 in 2001. But, it is also likely that workload pressures are a key contributing factor. The FDA managers, who determine when an advisory committee should be held, commented in interviews that the current time goals can discourage the use of advisory committees. Furthermore, we estimated that the percentage of approved new drugs that had an advisory committee decreased from 19 percent in 1998 to 12 percent in 2001 (see Table 6 in Appendix F).



Advisory committees compress the time allowed for reviewers to complete their evaluations. Several reviewers estimated that planning and conducting an advisory committee meeting takes about 2 months, in part due to requirements for public disclosure. When planning for a meeting, FDA is required to prepare and submit relevant materials to the advisory committee staff 19 days in advance of the meeting. This allows time for the materials to be distributed to advisory committee members and the public. The preparation for an advisory committee meeting compels reviewers to conduct their reviews earlier in the process in order to meet the time goal. Furthermore, meetings must

be scheduled early enough in the process to allow time afterward for reviewers to consider the committee's input. This can be particularly challenging for priority reviews.<sup>5</sup>

To help address this issue, PDUFA III calls for FDA to issue guidance on good review management principles. One of the areas that this guidance will address is anticipating and planning for an advisory committee meeting.

### **Workload pressures make it difficult to raise scientific disputes.**

It is important that reviewers have the opportunity to raise scientific disagreements, as they can help to raise critical questions about the safety and efficacy of a drug and can lead to more comprehensive reviews. For the 15 new molecular entities approved in FY 2001, we found one documented disagreement. We also found that some reviewers have concerns about raising disagreements. In fact, 21 percent of FDA survey respondents indicated that the work environment allowed for the expression of differing scientific opinions to a small or no extent. Similarly, an internal survey conducted by CDER of its reviewers found that one-third of respondents did not feel comfortable expressing their differing opinions. And, on our own survey, 18 percent of respondents indicated that they have felt pressure to approve or recommend approval for a drug, despite reservations about its safety, efficacy, or quality. Reviewers may be reluctant to raise disagreements because they fear slowing down the review process. The FDA's current procedures for handling disputes lack timelines for handling them.

### **Workload pressures contribute to staff turnover.**

An internal survey conducted by CDER of reviewers found that 50 percent of respondents indicated that their workloads are influential reasons to consider leaving FDA. According to FDA's analysis, medical officers and pharmacologists had the highest attrition rates within CDER in FY 2001, 8.4 percent and 6.9 percent respectively, compared to the overall average attrition rate for reviewers of 5.5 percent.<sup>6</sup> Many reviewers leave for private industry, which largely includes the pharmaceutical industry. The CDER officials indicated that often they cannot compete with the salaries offered by private industry. According to another CDER analysis, 26 percent of CDER's employees went to private industry in FY 2000 and 24 percent in FY 2001.<sup>7</sup> Hiring and training new reviewers adds to reviewers' workloads and can take time away from review activities.

The FDA has taken numerous steps to reduce turnover. For example, in October 2000, FDA implemented a pilot program to pay pharmacologists and statisticians a retention allowance of up to 10 percent of their basic pay.

## **Workload pressures curtail time for professional development.**

Staying abreast of scientific developments is essential to reviewer performance. In the meetings we observed between FDA and sponsors, the sponsors' consultants often included leading researchers in their fields who are aware of the latest research that bears on the sponsor's drug development plans. They and other sponsor representatives often posed questions to reviewers that called for the reviewers to be equally informed of the current research and its implications. In our interviews with reviewers, they emphasized to us how vital it is for them to find time to stay abreast of the latest developments in their disciplines.

Fifty-nine percent of FDA survey respondents indicated that they have little time to participate in professional development activities. An internal survey conducted by CDER of its reviewers obtained similar results; it found 60 percent of respondents did not feel that they had adequate time for professional development activities. The seriousness of this issue is further illustrated by that same CDER survey that found 25 percent of respondents regarded insufficient time for professional development as a reason to consider leaving FDA.

The FDA has taken several steps to encourage reviewers to participate in professional development activities. The FDA has a policy in place to allow reviewers to spend up to one day a week participating in professional development activities. The FDA has also developed and implemented an extensive internal training program that includes a broad range of classes from statistics to technical writing from which reviewers can choose.

## **Workload pressures allow little opportunity for reviewers to conduct research on drug development.**

From its review of investigational drug development plans of sponsors and of submitted NDAs, FDA has a unique repository of information concerning drug development. The FDA reviewers emphasized to us that this repository affords valuable potential that could be highly instructive to future drug development efforts. It could, they note, help guide clinical trial designs and help identify possible safety concerns that might be more fully addressed as part of the drug development process.

The CDER does award small grants to reviewers to conduct research on drug development through its Regulatory Science and Review Enhancement Program. The program has about \$250,000 of annual funding and funded about 21 projects in FY 2002. But, as we noted with respect to professional development, the time available for reviewers to conduct such research, without compromising their core review responsibilities, is limited.

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## **Several factors have contributed to the workload pressures.**

### **Tight deadlines.**

Although time goals have been beneficial, they place reviewers under constant pressure to meet deadlines. Reviewers conduct multiple activities, many of which have time goals attached. The same reviewers of NDAs also must review clinical trial designs, prepare for meetings with sponsors, and review supplements to approved NDAs. This pressure has increased as the goals have become progressively more challenging each year as required under PDUFA II. For example, in FY 1998, FDA's goal was to review and act upon 90 percent of standard NDAs within 12 months. In FY 2002, the goal was for FDA to review and act upon 90 percent of all standard NDAs within 10 months (see Appendix C).

### **Staffing limitations.**

Ninety-one percent of FDA survey respondents indicated that their workloads contribute to delays. Forty percent of FDA respondents who had been at FDA at least 5 years indicated in our survey that the review process had gotten worse in terms of allowing for an in-depth review. Lack of staff was a common explanation offered by those respondents. Reviewers raised concerns about the need to work overtime to complete their work on time.

The FDA cannot quickly reallocate its current staff to better accommodate changes in its workload. Workloads can vary by division, and staffing patterns do not always match up to the current workload. Administrative barriers to reassigning staff make it difficult to quickly adjust. Furthermore, FDA has difficulty estimating its workload from year to year. The FDA's workload depends largely on what sponsors submit. The FDA does attempt to estimate the number of NDAs that sponsors will submit through discussions with industry.

As we have already pointed out, PDUFA III acknowledges the limited staffing and calls for FDA to receive more resources to be used to hire additional reviewers. The CDER estimates it will hire close to 300 additional employees over the next 5 years using funds from user fees. This will help to alleviate some of the workload pressures.



## **Expectations to serve as an advisor to sponsors as well as a reviewer of new drug applications.**

Reviewers' dual roles as advisors and reviewers demand substantial time and resources and contribute to workload pressures. The CDER conducted 1,021 formal meetings with sponsors in FY 2001, mostly during the investigational new drug stage, prior to the NDA review process, when FDA provides advice. When a sponsor's request is determined to require a meeting, which was the case for 94 percent of requests in FY 2001 according to FDA, it has 14 days from the receipt of the request to schedule the meeting date. The FDA's analysis of data from CDER and the Center for Biologics Evaluation and Research found that the total hourly commitment for staff for a typical meeting ranges from about 124 to 543 hours.<sup>8</sup> Reviewers expressed concerns about the amount of time these meetings require.

During the investigational new drug stage, FDA provides advice and information in meetings with sponsors, based on an analysis of research plans or preliminary data. This advice is intended to improve the drug development process by ensuring that research is well designed, is well conducted, and results in pertinent data. Once research is complete and the application for a new drug is submitted, FDA reviewers continue to interact with the sponsor, not just as advisors, but as reviewers as well. The FDA is responsible for conducting an impartial review that will produce sufficient evidence to justify an approval or other decision.

The FDA's duties as advisor and reviewer are not necessarily conflicting, but the dual roles do add complexity and call for careful attention to boundaries. On the one hand, FDA must work with sponsors as partners, helping them to develop well-designed clinical trials and well-supported NDAs. On the other hand, it must function as an impartial reviewer of these NDAs on the public's behalf. The PDUFA III calls for FDA to develop guidance on good review management principles that will include advice on how to communicate with sponsors during the review process.

## **Shortcomings in some new drug applications.**

Incomplete NDAs contribute to delays in the review process. The 15 drugs we reviewed contained, on average, 38 amendments to the original application. Combined, the 15 drugs had 679 minor and major amendments. Of those amendments, the four most common types were: minor clinical (21 percent), minor chemistry (20 percent), minor multi-disciplinary (11 percent), and minor labeling (10 percent).

Some amendments are expected as reviewers raise questions during their reviews. But a large number of amendments, especially ones that contain key information, can cause

delays. Out of the 15 drugs we reviewed, 11 contained an amendment that FDA classified as major. None of those 11 drugs were approved in one review cycle. (FDA defines a major amendment as a submission from a sponsor that requires an extension of the time goal. The extension can vary from 45 days to 180 days, depending on the amount and type of information contained in the amendment.) According to 77 percent of FDA survey respondents, amendments that sponsors submit without a request from FDA contribute to delays. Similarly, when FDA requests an amendment, 91 percent of FDA respondents reported that waiting for sponsors contributes to delays.

Given the large size of NDAs, disorganization also can create delays in the review process and leads to additional amendments. When NDAs are disorganized, reviewers must spend time reorganizing information or request that sponsors submit amendments in the proper format, both of which can cause delays. Ninety percent of FDA survey respondents indicated that they spend time reorganizing data in NDAs. Common concerns include: improperly formatted data, missing information, incorrect analyses, unedited data sets, large amounts of irrelevant data, inconsistent tables, and difficult-to-locate materials.

Although FDA can refuse to file applications, it rarely does so. The CDER refused to file 4 percent of submitted applications in FY 2000, down from 17 percent in 1993. In part, this decrease may be attributable to the advice FDA provides sponsors that helps them prepare higher quality applications. However, reviewers commented that FDA accepts some applications that it should not accept. One reviewer characterized FDA as a “victim of its own kindness,” referring to the time and effort required to assess and integrate so many amendments after it files an application that it should have refused. Even one application filed that should have been refused can have significant consequences for FDA’s workload. Once filed, FDA must take time to document the deficiencies and provide advice to sponsors on what to include if the sponsor chooses to resubmit the application.

### **Concerns about inefficiencies in the review process.**

As we have already pointed out, FDA has taken numerous steps to enhance efficiency in the process. However, inefficiencies still remain, and they can contribute to workload pressures. Reviewers commented that they do not receive documents quickly enough. It can take days and sometimes weeks for documents to be routed to them. Many reviewers were concerned that they spend too much time handling administrative or basic research tasks that could be more easily addressed by others. For example, several of the scientific reviewers indicated that they spend time scanning documents into the computer, conducting basic literature searches, creating simple charts and tables, and preparing correspondence to sponsors.

Sponsors also raised concerns about inefficiencies. They were concerned that reviewers do not start their reviews soon enough, creating bottlenecks later in the process. Sponsors suggested that if FDA communicated the deficiencies earlier, they could prepare the materials so that all the information FDA needs would be available when the actual review took place. Sponsors were also concerned about inconsistencies in the process. Seventy-five percent of sponsors responding to our survey indicated that FDA reviews are inconsistent across the 15 review divisions within CDER. One sponsor commented that these inconsistencies may prompt some sponsors to shop for review divisions when a drug could be classified under different therapeutic review divisions.

The FDA has conducted few efforts to identify and eliminate inefficiencies in the review process. Forty-eight percent of FDA survey respondents indicated that FDA was not doing enough quality improvement activities. The FDA lacks estimates of how long it takes reviewers to conduct their various activities, and has not conducted a comprehensive review to identify areas of bottlenecks. In 2001, CDER established the Review Standards Staff to lead quality improvement efforts.

The PDUFA III calls for FDA to take numerous steps aimed at improving efficiency. Most notably, FDA will examine first-cycle reviews to determine best practices that facilitate a timely review. It calls for FDA to develop good review management principles that will include guidance on completing primary reviews early enough in the process to allow for sufficient deliberations. The PDUFA III calls for FDA to set aside \$7 million from users fees to conduct a wide range of studies aimed at fostering efficiency and effectiveness.

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## **Other factors also challenge the effectiveness of the new drug application review process.**

### **Rush to finalize labels at the end of the review cycle.**

Labels, which FDA approves as part of the NDA review process, are a key leverage point for FDA. The label provides the parameters on how a company can market a drug and provides key information concerning its safe and effective use, such as indications, dosages, contraindications, warnings, and precautions.<sup>9</sup> Both FDA respondents and sponsors were confident in the labeling decisions FDA makes, 70 and 81 percent respectively, indicated as such on our surveys.

However, we found that labeling negotiations are considerably rushed at the end of the review process and can occur right up to the day the drug is actually approved. To some extent, labeling negotiations must occur toward the end of the review process, after

reviewers have evaluated the data in the NDA and are familiar with the drug's efficacy and safety, but it appears to be too compressed. For the 15 new molecular entities we reviewed, we found that 27 percent of labeling amendments were submitted in the last 14 days. Eighty-two percent of FDA respondents indicated on our survey that the labeling negotiations can contribute to delays. Labeling negotiation can even lead to another review cycle. FDA's analysis of 26 new molecular entities approved by CDER between January 1, 2000, and October 31, 2001, found 2 drugs that were not approved in one review cycle primarily due to labeling.

The rush to finalize labels at the end may be in part caused by the lengthy negotiations that can occur between FDA and the sponsor over the label. Some of this interaction reflects the different perspectives of each. Sponsors are looking to obtain the best position to market their drugs, as the label serves as the legal basis from which they can advertise their drugs. Sponsors may also be concerned with liability issues and may want to list every possible adverse event. The FDA is primarily concerned with ensuring that the label provides useful information to health care professionals. Tension can erupt between what information is clinically significant versus what information is important for advertising and liability purposes.

The PDUFA III will help to address this issue. It calls for FDA to develop guidance on good review management principles. This guidance will address labeling feedback, including planning and holding meetings regarding labeling in advance of the time goal. In addition, FDA has several other efforts underway to further help alleviate the pressures associated with labeling negotiations. The FDA has proposed new regulations for the content and format of drug labels that make more explicit FDA's expectations and call for key information to be prominently displayed in a new highlights section.<sup>10</sup> The FDA issued two draft guidance documents regarding the adverse event section and the clinical studies section of labels that clarify what information sponsors should include in those areas.<sup>11</sup> The FDA proposed new regulations requiring sponsors to submit labels in electronic format to facilitate the creation of a labeling database that would make it easier to compare labels. Finally, FDA has a pilot project called Targeted Product Information that allows sponsors to submit a draft label to FDA at any time throughout the drug development process to help focus labeling discussions earlier in the process.

### **Uncertainty about the types of postmarketing commitments to request of sponsors.**

The ability to influence the postmarketing commitments made by the sponsor represents another key leverage point for FDA. As part of its approval decisions, FDA can request that sponsors commit to specific activities to manage the risks associated with their drugs. The most typical postmarketing commitment requested by FDA is to conduct additional

studies after the drug is on the market to further define its safety and efficacy. When a drug raises serious safety concerns, FDA can also request that sponsors establish patient registries, restrict distribution to certain populations, and/or ensure patients receive counseling from a pharmacist. According to a recent FDA report submitted to Congress, between 1991 and 2001, FDA approved 1,090 NDAs and sponsors agreed to conduct 2,328 postmarketing studies. That same report found that as of February 8, 2002, sponsors had completed 882 of the 2,400 postmarketing commitments on file at FDA for drugs.

Postmarketing commitments are critical given that FDA does not know all the risks associated with a drug at the time of its approval. Reviewers commented that they are often unsure what types of postmarketing commitments to request of sponsors. Little empirical evidence is available that demonstrates the effectiveness of these commitments. Sponsors were also unsure how FDA determines what types of commitments to request of sponsors.<sup>12</sup> Sixty-six percent of FDA respondents indicated on our survey that they were somewhat or not at all confident that FDA adequately monitors the safety of prescription drugs once they are on the market.

The FDA has already taken numerous steps to help address this issue. In part due to a 1996 OIG study, *Postmarketing Studies of Prescription Drugs* (OEI-03-94-00760), that found FDA lacked formal standards to track these commitments, FDA has put in place new policies and procedures to better track these commitments. The PDUFA III also gives considerable attention to the issue of postmarketing commitments. First, it calls for FDA to hold meetings with sponsors prior to the submission of the NDA to review and discuss sponsors' preliminary risk management plan. Second, it calls for FDA to review sponsors' proposed risk management plans as part of an NDA. Third, it allows FDA to use funds from user fees to review sponsors' implementation of the risk management plans for a period of up to 2 years, and up to 3 years for products that require risk management beyond standard labeling. Finally, it calls for FDA to issue three guidance documents addressing risk assessment, risk management, and pharmacovigilance practices that should help to provide some clarity on FDA's expectations.

### **Limited disclosure to the public about the basis of key decisions concerning new drug applications.**

**No summary basis for approval.** We reviewed information on CDER's website regarding the 15 new molecular entities approved in FY 2001, and in no case did it provide a summary document that explains the overall basis for the approval. It does not routinely provide this type of summary information nor is it required to do so.<sup>13</sup> The lack of this summary information makes it difficult for sponsors and the public to understand the criteria FDA uses to make its decisions. FDA does provide technical information on

its website on approved drugs, but it consists of hundreds of pages of highly scientific documents for each drug. The FDA also posts approval letters on its website. However, they are largely administrative documents.

**Drug approval documents are not promptly disclosed on FDA’s website.** We found that it took CDER 7.6 months after the date of approval, on average, to post reviewer evaluations on its website for the 15 drugs we reviewed. The FDA’s goal is to have the reviewer evaluations and other technical documents, such as the label and approval letter, posted on its website within 6 weeks of approval. Redacting proprietary information and waiting for reviewers to compile their documentation into a formal package after the drug has been approved can cause delays.

**Limited disclosure about FDA’s decisions not to approve drugs.** When FDA decides not to approve a drug, it issues one of two types of action letters: an approvable or non-approvable letter. These letters explain in detail the deficiencies FDA found with the application. However, approvable letters are not disclosed to the public at the time they are issued, and non-approvable letters are almost never disclosed. The FDA regulations limit the public disclosure of approvable and non-approvable letters. An approvable letter is disclosed to the public if the drug is later approved, which can be months or years after the letter was issued. As a result, the public remains largely unaware of FDA’s rationale for not approving drugs.

# CONCLUSION

Our review of FDA's NDA review process disclosed that it has several strengths that contribute significantly to its effectiveness. Both reviewers and sponsors have confidence in the decisions FDA makes. Review times have dropped considerably. The FDA works collaboratively with sponsors and has taken several steps to enhance efficiency. But we also found that workload pressures increasingly challenge the effectiveness of the process. For example, 40 percent of FDA survey respondents who had been at FDA at least 5 years indicated that the review process had worsened during their tenure in terms of allowing for in-depth, science-based reviews. Respondents cited lack of time as the main reason. Reviewer concerns about time goals do not mean that there is a threat to public health, but they do indicate a significant management issue warranting attention. These pressures can also discourage the use of advisory committees, inhibit the raising of scientific disputes, reduce the time available for professional development, and contribute to staff turnover.

Three other factors also challenge the effectiveness of the review process: (1) the rushed review of drug labels toward the end of the review process, (2) the limited guidance available to reviewers in determining the extent and the type of postmarketing commitments to request of sponsors, and (3) the limited information that FDA makes available to the public on the basis for its decisions concerning NDAs. Considered as a whole, our findings present a significant warning signal, one that could jeopardize gains FDA has made in recent years, if not fully addressed.

We recognize that FDA has already identified many of the concerns presented in this report and has numerous efforts underway to address them. In particular, the enactment of PDUFA III, which FDA played a critical role in developing with sponsors, presents significant opportunities to address many of our findings. It calls for an increase in user fees that will allow FDA to hire close to 300 additional employees. Over time, this could help considerably in relieving the workload pressures that we have emphasized. In addition, PDUFA III calls for FDA to conduct various activities that will address efficiency, consistency, labeling negotiations, and the use of advisory committees. It calls for significant attention to be placed on postmarketing commitments, by allowing user fees to be used to monitor drugs after they are on the market. It also calls for FDA to issue guidance on developing risk management plans.

Our first recommendation offers additional steps for FDA to take as it implements PDUFA III to ensure that the agency takes full advantage of its opportunities. Although PDUFA III presents opportunities, other issues still remain. Accordingly, our last four recommendations outline additional actions that FDA can take to improve the NDA process. We direct all our recommendations to CDER.

# RECOMMENDATIONS

## 1. Take full advantage of the opportunities in PDUFA III.

- ▶ Conduct a retrospective examination of recent reviews to determine the capacity of reviewers to conduct in-depth, science-based reviews. Make this review a part of the \$7 million performance management fund that PDUFA III establishes. Include in this review drugs that were approved, as well as those that were not; different review divisions; and an assessment of the completeness and organization of applications submitted by sponsors.
- ▶ Evaluate the adequacy of current staffing levels and the workload distribution among the 15 review divisions within CDER, and implement a system that in real time would indicate the status of an application and the time spent in reviewing its specific parts. Conduct this evaluation as part of the comprehensive process review and analysis that PDUFA III requires FDA to undergo.
- ▶ Assess how amendments to the original application, internal processing delays, and labeling negotiations affect FDA's capacity to make timely, first-cycle review decisions. Include this assessment as part of the examination of first-cycle reviews that PDUFA III requires.
- ▶ Examine how continuous marketing applications affect not just the efficiency, but also the quality of the review process. The PDUFA III requires FDA to conduct a pilot project to test the concept of continuous marketing applications that involves FDA reviewing sections of an application prior to the submission of the complete application.
- ▶ Provide a guidance document for reviewers addressing the scope of the filing review and monitoring the effect that early notification to sponsors has on reviewer workloads. The PDUFA III requires FDA to notify sponsors within 14 days after the filing review of any deficiencies it has noted thus far in the application.
- ▶ Offer further guidance on the best way to handle scientific disputes that occur among reviewers and how to balance the role of reviewing NDAs and the role of providing advice to sponsors concerning those applications. Provide this guidance as part of the good review management principles that PDUFA III requires FDA to develop and implement.



- ▶ Include case studies of past reviews as part of the training on good review management principles that PDUFA III requires. Case studies serve as a way to illustrate good review principles and foster consistency among divisions.
- ▶ Provide a list of the various postmarketing commitments that reviewers can request of sponsors and suggestions for when each could be considered. Include this as part of the risk management guidance documents that PDUFA III requires. In making suggestions on when to use each tool, take into account the population most likely to be using the drug, the severity of the disease, and drug interactions.

## **2. Determine whether the significant workload pressures discussed in this report justify any exceptions to the current time goals regarding new drug applications to allow for more in-depth reviews.**

As we have indicated, the Prescription Drug User Fee Act and the FDA Modernization Act have been positive forces for the review process. They have fostered a productive, collaborative relationship between FDA and sponsors, a more expeditious drug development and review process, and a more efficient and systematic review process within FDA. Yet, it is important that an appropriate balance exists between timeliness and comprehensive reviews. Our data show that reviewers have concerns about the amount of time available to conduct their reviews, and this is an important management issue warranting attention. Accordingly, FDA could examine further if it would be beneficial to extend the review clock, perhaps by 1 or 2 months, when it chooses to use an advisory committee. Also, it could examine if it would be beneficial to modify the current 10-month time goal for standard NDAs perhaps by 1 or 2 months. Some moderation in time goals could help to reduce workload pressures and lead to fewer review cycles.

## **3. Reject applications that are incomplete and of poor quality that can create delays in the new drug application review process.**

Toward that end, FDA could reexamine its policies regarding refusal-to-file decisions to ensure that they are adequately explicit. It could ensure that all review divisions within CDER appropriately apply its policies. It could also examine its current guidance to sponsors on submitting applications to ensure that it makes clear FDA's expectations.

#### **4. Provide the public with a clear and timely explanation of decisions on new drug applications.**

Disclosure is particularly important given that so much of the process is closed to the public and that industry pays for these reviews. We recommend two directions that FDA take to enhance public disclosure.

The FDA could include on its website, within a month, if possible, a succinct explanation of its rationale for approving an application. The agency is already moving in this direction by requiring reviewers to provide executive summaries as part of discipline-specific templates. These summaries could provide the basis for the overall summary. Such information would help convey to the public, as well as to sponsors, the criteria FDA uses in making its decisions. Over time, this could lead to improved drug applications.

The FDA could provide the same public explanation on a timely basis when it decides not to approve an application. We recognize that this will likely require regulatory changes. The rationale for FDA's decision could be conveyed in ways that protect proprietary considerations. Disclosing such information would help convey to the general public the independent role that FDA plays in the review process, and that FDA does not approve all drugs.

#### **5. Conduct or support research that takes greater advantage of its vast clinical trial databases to identify ways to improve drug development.**

We found that FDA has little time to take advantage of its unique perspective on the drug development process. Accordingly, we recommend that FDA conduct or support research that takes greater advantage of its vast clinical trial databases to identify ways to improve drug development. We recognize that such research will use scarce resources, but, over time, the results could be highly cost-effective, contributing to better clinical designs and more efficient drug development.

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### **AGENCY COMMENTS**

The FDA reviewed a draft of this report, and overall, it concurred with our conclusions and recommendations. In its comments, FDA outlined numerous activities it has underway or planned to address our recommendations. Specifically, FDA indicated that it is reviewing its workload distribution and has studies underway to examine delays in the review process. The full text of FDA's comments can be found in Appendix A.

## Agency Comments



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration  
Rockville MD 20857

December 24, 2002

TO: Inspector General  
FROM: Commissioner of Food and Drugs  
SUBJECT: OIG Draft Report, "FDA's Review Process for New Drug Applications: A Management Review," OEI-01-01-00590

The Food and Drug Administration is pleased to provide comments on the OIG Draft Report. We are in complete agreement with the overall conclusions of the report: (1) the new drug application (NDA) review process is robust, but workload pressures increasingly challenge its effectiveness; and (2) the enactment of Prescription Drug User Fee Act (PDUFA III) presents significant opportunities to address many of the findings in the report.

The report states, "both FDA reviewers and sponsors have confidence in the decisions FDA makes." We believe the American public also has confidence in FDA's decisions and a high regard for the work of the agency. As stated in the OIG findings, the agency has met most of the goals outlined throughout the drug development process and taken steps to improve, through numerous activities, the efficiency and consistency in the process. The FDA has reduced significantly the application review and approval times and the drug development time. At the same time, the agency has maintained strong safety and effectiveness standards. Drug review and approval in the United States now represent the *international gold standard*.

Much of the report focuses on how workload pressures, generally related to pressures on review staff to meet time goals, increasingly challenge the effectiveness of the review process. We fully concur that the agency has been understaffed to meet user fee goals, particularly the multiple process goals imposed by PDUFA II. While fluctuating workload and time constraints will always create management problems, we agree that the additional resources allocated in PDUFA III will go a long way to address them. Concurring with the report, we also are very concerned about staff turnover. Despite the workload pressures, however, FDA remains a leader in *Quality of Worklife* measures.

The following are FDA's comments on the recommendations made in the report:

**1. Take full advantage of the opportunities in PDUFA III.**

- *Conduct a retrospective examination of recent reviews to determine the capacity of reviewers to conduct in-depth, science-based reviews. Make this review a part of the \$7 million performance management fund that PDUFA III establishes. Include in this review drugs that were approved and those that were not, different review divisions, and an assessment of the completeness and organization of applications submitted by sponsors.*

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**Comment:** A study was completed by CDER to review and better understand the cause for "delay" for drugs that took longer than 12 months to be approved in fiscal years 2000 and 2001. We are now working on a similar project for priority applications approved in fiscal years 2000, 2001, and 2002. CDER will consider using the PDUFA III first-cycle review external consultants to provide a study that would be both retrospective and prospective.

- *Evaluate the adequacy of current staffing levels and the workload distribution among the 15 review divisions within CDER and implement a system that in real time would indicate the status of an application and the time spent in reviewing its specific parts. Conduct this evaluation as part of the comprehensive process review and analysis that PDUFA III requires FDA to undergo.*

**Comment:** CDER is reviewing its workload/Full Time Equivalent distribution. We are awaiting more information regarding the CBER/CDER consolidation. The review will be completed early next year, as part of PDUFA III.

- *Assess how amendments to the original application, internal processing delays, and labeling negotiations affect FDA's capacity to make timely, first-cycle review decisions. Include this assessment as part of the examination of first-cycle reviews that PDUFA III requires.*

**Comment:** The study described in our first comment addressed portions of this recommendation. Additional assessments will be completed in the first-cycle review expert consultation study.

- *Examine how continuous marketing applications [CMA] affect not just the efficiency but also the quality of the review process. PDUFA III requires FDA to conduct a pilot project to test the concept of continuous marketing applications that involves FDA reviewing sections of an application prior to submission of the complete application.*

**Comment:** We will engage an outside consultant to review the CMA process. Part of that study will assess any impact on the quality of reviews.

- *Provide a guidance document for reviewers addressing the scope of the filing review and monitoring the effect that early notification to sponsors has on reviewer workloads. PDUFA III requires FDA to notify sponsors within 14 days after the filing review of any deficiencies it has noted thus far in the application.*

**Comment:** CDER is well along in its process of developing a Manual of Policies and Procedures on the filing review process and identifying and communicating issues to the sponsor of filed applications, as required under PDUFA III. As the agency establishes future long-term goals, additional process guidances will be considered.

- *Offer further guidance on the best way to handle scientific disputes that occur among reviewers and how to balance the role of reviewing NDAs and the role of providing advice to sponsors concerning those applications. Provide this guidance as part of the good review management principles (GRMP) that PDUFA III requires FDA to develop and implement.*

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**Comment:** These issues will be addressed in our GRMP guidance.

- *Include case studies of past reviews as part of the training on good review management principles that PDUFA III requires. Case studies serve as a way to illustrate good review principles and foster consistency among divisions.*

**Comment:** The agency agrees with this recommendation and will incorporate into its training.

- *Provide a list of the various postmarketing commitments that reviewers can request of sponsors and suggestions for when each could be considered. Include this as part of the risk management guidance documents that PDUFA III requires. In making suggestions on when to use each tool, take into account the population most likely to be using the drug, the severity of the disease, and drug interactions.*

**Comment:** This issue will be addressed in two of the PDUFA III Risk Management Guidances (Good Risk Assessment and Good Pharmacovigilance).

2. **Determine whether the significant workload pressures discussed in this report justify any exceptions to the current time goals regarding new drug applications to allow for more in-depth review.**

**Comment:** During the PDUFA III discussions, the agency discussed the value of extending the review clock by 2 or 3 months for a priority review application, which requires an advisory committee meeting. While industry was sympathetic to the difficult logistics of doing a 6-month review and preparing for an advisory committee meeting, we could not reach agreement. The value of such an extension must always be balanced against the perception that FDA would be “slowing down” or “taking more time” for the most important drugs we review.

The CMA pilot program for rolling review of Fast Track applications will provide some relief by allowing some priority reviews to start earlier. Also, resources under PDUFA III should enable the agency to increase the number of reviewers to ensure an application is reviewed promptly and goal dates are met. Also, PDUFA allows clock extensions for major amendments.

3. **Reject applications that are incomplete and of poor quality that can create delays in the new drug application review process.**

**Comment:** The agency will address this recommendation in the following ways: 1) additional staffing and guidance/procedures to ensure that End-of-Phase 2 and pre-NDA meetings generate good applications, 2) emphasize that applications are expected to be complete at the time of submission and that late-submitted data may not be reviewed during the review cycle; and 3) through expert consultant study of first-cycle reviews as required under PDUFA III.

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**4. Provide the public with a clear and timely explanation of decisions on new drug applications.**

- *FDA could include on its Web site, within a month, if possible, a succinct explanation of its rationale for approving an application.*

**Comment:** The agency agrees with the recommendation to provide a clearer and timely notification to the public of drug approvals on its Web site.

- *FDA could provide the same publication explanation on a timely basis when it decides not to approve an application.*

**Comment:** FDA does not have the authority to disclose that information. Providing public explanations application FDA does not approved or deems approvable would require regulatory and statutory changes.

**5. Conduct or support research that takes greater advantage of its vast clinical trial databases to identify ways to improve drug development.**

**Comment:** FDA supports this recommendation. Although funds are limited in this area, the agency currently provides grants to support projects as part of its Regulatory Science and Review Enhancement Program. This program focuses on two outcomes:

- (1) To help FDA's management and staff use the available information to reach CDER's regulatory objectives efficiently and effectively and in disseminating scientific information to the pharmaceutical industry for use in planning future drug trials; and
- (2) To support the growth of the agency's staff through professional development.

We appreciated your informative report, and concur with the overall conclusions. If you need additional information, please have your staff contact Loretta Davis, (301) 827-4809.

*by [Signature]*  
Mark B. McClellan, M.D., Ph.D.

## Glossary

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**Approvable:** An action assigned to the new drug application (NDA) at the end of the review process when problems exist with the application that need to be addressed before the drug product may be approved.

**Class I resubmission:** An application resubmitted after an approvable or non-approvable letter has stated deficiencies in the following areas: final printed labeling, draft labeling, safety updates, stability updates, phase IV commitments, assay validation data, final release testing on the last 1-2 manufacturing lots (used to support approval), minor reanalysis of data previously submitted to the application, and/or other minor clarifying information.

**Class II resubmission:** An application resubmitted after an approvable or non-approvable letter has stated other deficiencies not under a Class I resubmission including items that require an advisory committee meeting.

**Clinical hold:** A decision made by the Food and Drug Administration (FDA) to stop a clinical trial if there is reason to believe the study cannot be conducted without unreasonable risk to the human subjects enrolled in the trial. The sponsor must address FDA's concerns before the hold is lifted.

**Clinical trials or clinical studies:** A scientific study with human subjects to examine a drug's safety and efficacy.

**Drug development process:** The entire process of bringing a drug to market. The process includes laboratory and animal testing of the drug, the investigational NDA to FDA, the clinical trials, and finally the submission of the NDA to FDA for marketing approval.

**Efficacy supplement:** Additional efficacy data submitted by a sponsor to FDA for an already approved drug. FDA requires an efficacy supplement when a sponsor seeks approval for a new indication.

**Indications:** Symptoms or conditions that indicate a specific medical treatment. When FDA approves a drug it is approved for a specific indication(s) that is described on the drug's label.

**Investigational NDA:** An application submitted by a sponsor to FDA technically seeking exemption from the federal law that prohibits the shipping of an unapproved drug across state lines. The intent of the application is to provide data to FDA documenting that it is reasonable to begin clinical trials in humans with the drug. If FDA determines that the data are insufficient to proceed, it can place the trials on hold.

**Manufacturing supplement:** Information submitted by the sponsor to FDA on manufacturing changes to an already approved drug.

**New Drug Application (NDA):** An application submitted by a sponsor to FDA to obtain approval to market a drug in the United States.

**New molecular entity:** A drug that contains an active ingredient that has never been approved for marketing in the United States. It can be submitted as either a standard NDA or a priority NDA.

**Non-approvable:** An action assigned to the NDA when, at the end of the review process, significant deficiencies exist in the application that may require additional research on the drug product or reformulation of the drug product before the application can be approved.

**Primary reviewer:** An FDA employee who conducts the bulk of the review by evaluating the data in the NDA and recommends the action FDA should take on a drug. Primary reviewers include clinicians, pharmacists, pharmacologists, statisticians, microbiologists, and chemists.

**Priority NDA:** Priority applications are for drugs that are a significant improvement over drugs already on the market to treat the same condition.

**Project manager:** An FDA employee who manages the NDA by tracking the application's status and scheduling FDA internal meetings as well as meetings with sponsors. The project manager is a liaison between FDA and the sponsor.

**Postmarketing surveillance:** FDA's efforts to monitor the safety of a drug after it is on the market, which includes monitoring adverse event reports.

**Review clock:** The review clock is the time between FDA's receipt of the application and FDA's decision. The PDUFA III calls for FDA to review and act upon 90 percent of standard NDAs within 10 months and 90 percent of priority applications within 6 months.

**Review cycle:** The first review cycle is from FDA's receipt of the initial application to FDA's decision. Multiple review cycles occur when an application receives an approvable or non-approvable decision from FDA, and then the sponsor revises the application and resubmits it to FDA. When the sponsor resubmits the application, the review clock restarts and FDA receives either 2 or 6 months to review the revised application, depending on the information in the resubmission.

**Secondary reviewer:** An FDA employee who reviews the primary reviewer's work. Secondary reviewers include clinicians, pharmacists, pharmacologists, statisticians, microbiologists, and chemists.

**Sponsor:** A person or entity that is responsible for a drug's development. It can be an individual, government agency, or a pharmaceutical company.

**Standard NDA:** Standard applications are for all applications not classified as priority.

**Total approval time:** Total approval time is the time from the date of FDA's receipt of the original application to the date of the application's approval. This time can include multiple review cycles and the time spent by the sponsor revising the application between review cycles.



**Time Goals for FDA’s Center for Drug Evaluation and Research**

<b>Table 1. Time Goals for FDA’s Center for Drug Evaluation and Research</b> (M=met, F=failed to meet, N=data not yet available, and NA=not applicable)			
<b>Action</b>	<b>FY 2000</b>	<b>FY 2001</b>	<b>FY 2002</b>
1. Review and act on priority applications.	90% in 6 months (M)	90% in 6 months (M)	90% in 6 months (N)
2. Review and act on standard applications.	90% in 12 months (M)	90% in 12 months (N)	(NA)
3. Review and act on standard applications.	50% in 10 months (M)	70% in 10 months (N)	90% in 10 months (N)
4. Review and act on Class I resubmissions.	90% in 4 months (M)	(NA)	(NA)
5. Review and act on Class I resubmissions.	70% in 2 months (M)	90% in 2 months (F)	90% in 2 months (N)
6. Review and act on Class II resubmissions.	90% in 6 months (M)	90% in 6 months (M)	90% in 6 months (N)
7. Review and act on priority efficacy supplements.	90% in 6 months (M)	90% in 6 months (F)	90% in 6 months (N)
8. Review and act on standard efficacy supplements.	90% in 12 months (M)	90% in 12 months (N)	(NA)
9. Review and act on standard efficacy supplements.	50% in 10 months (M)	70% in 10 months (N)	90% in 10 months (N)
10. Review and act on manufacturing supplements, prior approval not required.	90% in 6 months (M)	90% in 6 months (M)	90% in 6 months (N)
11. Review and act on manufacturing supplements, prior approval required.	90% in 6 months (M)	90% in 6 months (M)	(NA)
12. Review and act on manufacturing supplements, prior approval required.	50% in 4 months (M)	70% in 4 months (M)	90% in 4 months (N)
13. Notify requestor of meeting within 14 days.	80% on time (M)	90% on time (F)	90% on time (N)
14. Schedule Type A meetings within goal date or within 14 days of requested date, if longer. Goal date is 30 days.	80% on time (M)	90% on time (F)	90% on time (N)
15. Schedule Type B meetings within goal date or within 14 days of requested date, if longer. Goal date is 60 days.	80% on time (F)	90% on time (F)	90% on time (N)
16. Schedule Type C meetings within goal date or within 14 days of requested date, if longer. Goal date is 75 days.	80% on time (M)	90% on time (M)	90% on time (N)
17. Prepare meeting minutes within 30 days of meeting.	80% on time (M)	90% on time (F)	90% on time (N)
18. Respond to sponsor’s appeal of decision within 30 days of receipt of sponsor’s appeal.	80% on time (M)	90% on time (M)	90% on time (N)
19. Respond to sponsor’s complete response to a clinical hold within 30 days of receipt of request.	90% on time (F)	90% on time (F)	90% on time (N)
20. Respond to sponsor’s request for an evaluation of protocol design within 45 days of protocol and evaluations.	70% on time (M)	80% on time (M)	90% on time (N)
<b>Source: FDA’s Center for Drug Evaluation and Research</b>			

## Highlights of PDUFA III

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In June 2002, user fees were reauthorized as part of the Public Health Security and Bioterrorism Preparedness Act of 2002. The part of the Act addressing user fees is referred to as PDUFA III. Below, we highlight the provisions within PDUFA III that have the most relevance to our inquiry.<sup>14</sup>

### Increased resources

According to a press release from the U.S. Department of Health and Human Services “the law puts PDUFA III on sound financial basis.”<sup>15</sup> The PDUFA III calls for an increase in user fees. In FY 2002, FDA, including both the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research (CDER), estimates that it will collect approximately \$160 million in user fees. The PDUFA III increases the total funds from these fees to about \$223 million in FY 2003, and gradually increases it over the next 5 years, to about \$260 million in FY 2007. With these funds, CDER estimates that it will hire close to 300 employees over the next 5 years. The funds will also be used to improve CDER’s computer infrastructure.

### Time goals

All existing time goals for FY 2002 for reviewing key documents and other administrative tasks remain in place under PDUFA III (see Appendix B for the current time goals). In addition, it adds four new goals.

The first two new goals are for resubmitted efficacy supplements. The FDA will review and act on Class I resubmitted efficacy supplements within 6 months for 90 percent of supplements in FY 2003 and for 30 percent of supplements within 2 months. By FY 2007, the goal increases to 90 percent within 2 months. The PDUFA III also calls for FDA to review and act on Class II resubmitted efficacy supplements within 6 months of receipt. This goal remains constant over the next 5 years.

The third new goal is for notifying sponsors of issues identified during the filing review. FDA will notify the sponsor within 14 days after the 60-day filing review of any deficiencies it has noted thus far in the application. It will meet this goal date for 50 percent of applications in FY 2003, 70 percent in 2004, and 90 percent in FY 2005, 2006, and 2007.

The fourth new goal applies to reviewable units, which we address below.

### **Studies to improve the management of the process**

The PDUFA III calls for FDA to set aside \$7 million from user fees to undertake initiatives to improve the drug review process. These studies are intended to foster improvement in many areas, such as professional development, consistency, efficiency, effectiveness, and improved communication.

One of these studies will seek to evaluate FDA's first-cycle review performance and the impact of good review management principles. This assessment will examine all first-cycle reviews and identify best practices that allow for more efficient reviews. Another study will be a comprehensive process review and analysis that examines review management.

### **Pilot programs to test the concept of continuous marketing applications**

The PDUFA III calls for FDA to conduct two pilot projects to determine whether early review of sections of new drug applications and additional feedback with sponsors throughout the drug development process lead to faster review times. The FDA will hire a consultant to evaluate each pilot project.

Under the first pilot project, FDA will review a complete section of an NDA separately, prior to the submission of the entire application, in reviewable units. Each reviewable unit will have its own review time of 6 months. This pilot project only applies to fast-track drugs, which are drugs intended to treat serious or life-threatening illnesses and demonstrate the potential to meet an unmet medical need. Between 1998 and 2001, FDA approved 12 fast-track drugs.

Under the second pilot project, FDA will enter into an agreement with a sponsor to provide feedback and interaction throughout the drug development process. This pilot project is also limited to fast-track drugs and further limited to one agreement with a sponsor per review division.

## Good review management principles

The PDUFA III calls for FDA to develop guidance on good review management principles that addresses the filing review process, communication with sponsors, planning for advisory committee meetings, primary review completion, and labeling feedback. The FDA will also develop and implement a training program for new and current employees on these good review management principles.

## Guidance on risk management practices

For the first time, PDUFA III allows FDA to use funds from user fees towards postmarketing surveillance. The FDA anticipates hiring additional postmarketing reviewers.

The PDUFA III calls for several new initiatives related to improving risk management. One of these is a package sponsors may submit prior to the submission of a new drug application that contains the sponsors's anticipated risk management plan and safety assessment for the drug. This package serves as the basis for a meeting between FDA and the sponsor to discuss the safety profile and the risk management plan for the drug. The FDA will accept and review risk management plans as part of a new drug application and will communicate, as early in the process as practicable, any safety issues that must be addressed in order to obtain approval. After the drug is approved, FDA will review the sponsor's implementation of the risk management plan for 2 to 3 years, referred to as the periapproval period, and will require safety reports during this period.

Finally, FDA will issue guidance to address good risk assessment, risk management, and pharmacovigilance practices. And, FDA will inform the public if sponsors fail to complete their postmarketing commitments.

## Additional efforts

The PDUFA III calls for the simplification of action letters. The FDA will move towards two types of action letters, approval and complete response, instead of the three types it currently uses — approval, approvable, and non-approvable. It calls for each reviewer to submit an information request letter immediately after an initial review that lists the deficiencies. It calls for an extension of the goal date by 3 months, when a sponsor submits a major amendment to an original application, efficacy supplement, or resubmission within 3 months of the goal date.

### Rate of Withdrawn Drugs

Figure 2 shows the percentage of new molecular entities withdrawn by the calendar year of their approval. The PDUFA was first implemented on 10/1/92. Data for calendar year 2002 is as of 4/30/02.

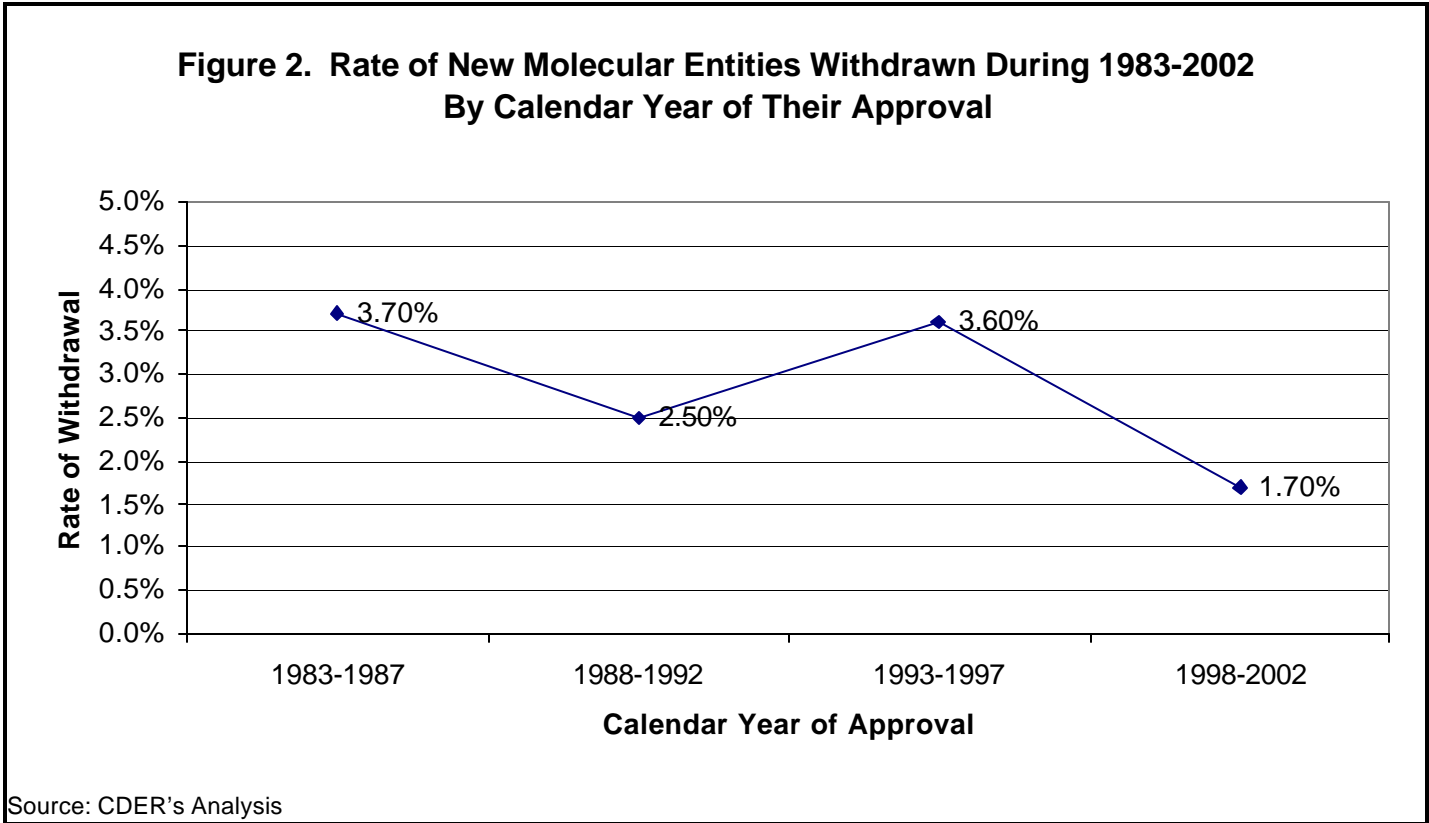
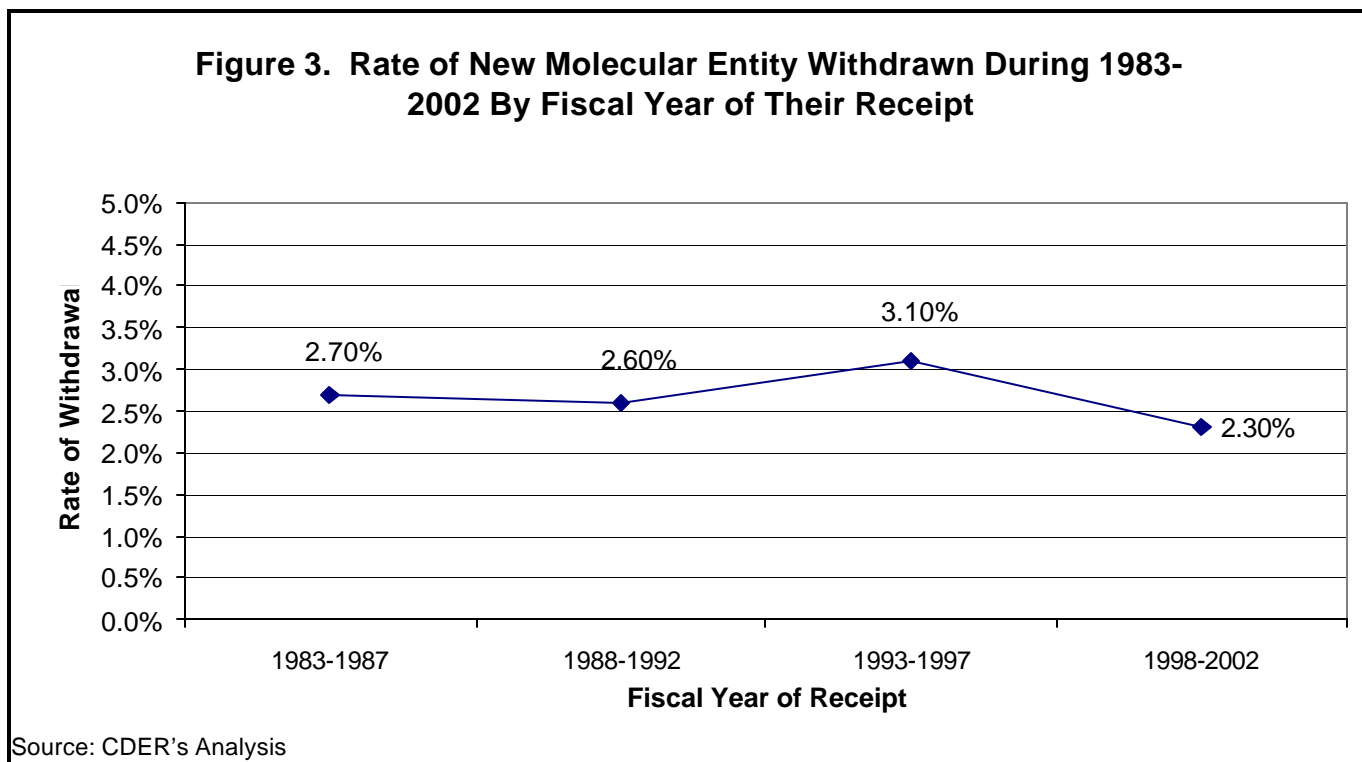


Figure 3 shows the percentage of new molecular entities withdrawn by the fiscal year of their receipt. The PDUFA was first implemented on 10/1/92. Data for calendar year 2002 is as of 4/30/02.



## Methodology

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### Survey of CDER Reviewers

We created a web-based survey for CDER officials using Raosoft EZSurvey® software. We pretested the survey with several CDER reviewers and managers. The CDER hosted the survey on its Intranet. We sent an e-mail notifying all employees within CDER about our survey indicating the individuals who should participate. We asked for all primary, secondary (e.g., team leader) and tertiary reviewers (e.g., division director) across all review disciplines including postmarketing divisions to fill out the survey. The survey was voluntary and anonymous, unless respondents chose to disclose their name and contact information. Respondents could also print out the survey to send directly to our office or request a copy be sent to them. We sent one reminder electronically midway through the collection period.

We used EZSurvey® software to tabulate the results of the survey. Based on numbers obtained from CDER, we estimated that 846 reviewers were eligible to complete the survey. After removing 2 duplicates, we received a total of 401 responses to our survey, yielding an estimated response rate of 47 percent. (See Tables 2 - 4 for descriptive information on the CDER respondents.) We tabulated the results by the length of service of the respondent; the level of the respondent i.e., primary, secondary, or tertiary reviewer; and the scientific discipline of the respondent. We were unable to do a non-respondent analysis since the survey was anonymous.

This survey had three main limitations. First, non-responses may have occurred because of technical problems using the web-based survey. Some respondents complained that the website disconnected while they were filling out the survey. Second, although our survey was anonymous and we did not collect the Internet Protocol (a computer's address), which could indirectly identify the respondent, some respondents may have not participated out of concerns for their anonymity. Third, although survey access was limited to CDER employees, the potential exists that some individuals not in our intended population completed the survey.

<b>Table 2. Number of CDER Respondents by Review Discipline</b>		
<b>Review Discipline</b>	<b>No. of CDER Respondents</b>	<b>Percent of CDER Respondents</b>
Blank	5	1%
Chemistry, Manufacturing, and Controls	48	12%
Clinical	107	27%
Clinical Pharmacology, Biopharmaceutics, Pharmacology, and Toxicology	96	24%
Labeling Reviewer (Division of Drug Marketing, Advertising, and Communications)	14	3%
Microbiology (product quality and clinical efficacy)	13	3%
Pharmacovigilance	12	3%
Regulatory Project Management	46	11%
Statistics	38	9%
Trade Name Reviewer (Office of Drug Safety)	6	1%
Other	16	4%
<b>TOTAL</b>	<b>401</b>	<b>100%</b>
Source: OIG Survey of CDER Officials		



<b>Table 3. Number of CDER Respondents by Level of Reviewer</b>		
<b>Level of Reviewer</b>	<b>No. of CDER Respondents</b>	<b>Percent of CDER Respondents</b>
Blank	13	3%
Primary reviewer	265	66%
Secondary reviewer	64	16%
Tertiary reviewer	23	6%
Other	36	9%
<b>TOTAL</b>	<b>401</b>	<b>100%</b>
Source: OIG Survey of CDER Officials		

<b>Table 4. Number of CDER Respondents by Length of Service at CDER</b>		
<b>Length of Service at CDER</b>	<b>No. of CDER Respondents</b>	<b>Percent of CDER Respondents</b>
Blank	34	8%
0-4 years	143	36%
5-9 years	134	33%
10 or more years	90	22%
<b>TOTAL</b>	<b>401</b>	<b>100%</b>
Source: OIG Survey of CDER Officials		

**Internal CDER Survey**

In this report, we also present data from a survey conducted by CDER of its reviewers in September 2000. The CDER mailed the survey to a random sample of 188 reviewers (i.e, medical, statistical, pharmacology/toxicology, biopharmacology, and chemistry) in numbers proportional to those of their scientific disciplines across CDER. It received a 72 percent response rate (N=136).

**Survey of Sponsors**

We mailed a survey to all sponsors, excluding one federal agency, that had at least one NDA approved by CDER in the calendar years 1999, 2000, and 2001. We obtained the list of companies and their addresses from FDA and removed any duplicates that we were able to identify, for a total of 119 sponsors in our population. We addressed the survey to the chief executive officer and/or senior regulatory official within the sponsor’s organization. The survey was voluntary and anonymous, unless respondents chose to disclose their name and contact information. We sent a reminder to all sponsors midway through the collection period. Sponsors returned the survey in the enclosed self-addressed envelope or by fax. We manually entered the responses into Raosoft EZSurvey® software for analysis. We received 72 responses, yielding a response rate of 60 percent. (See Table 5 for more information on the sponsor respondents.) We were unable to do a non-respondent analysis since the survey was anonymous.

<b>Table 5. Number of Sponsor Respondents by the Number of Approved NDAs</b>		
<b>Total No. of NDA’s Approved Between 2001-1997</b>	<b>No. of Sponsor Responses</b>	<b>Percent of Sponsor Responses</b>
Blank	2	3%
1 NDA	21	29%
2-5 NDAs	38	53%
More than 5 NDAs	11	15%
<b>TOTAL</b>	<b>72</b>	<b>100%</b>
Source: OIG Survey of Sponsors		

The survey had three main limitations. First, the survey was not addressed to a specific individual, so it may not have been delivered to the appropriate official. Second, the list of identified sponsors may include a parent company and its subsidiaries that could lead to multiple responses by the same company. Lastly, several surveys were undeliverable because of inaccurate contact information.

## **File Review of New Molecular Entities**

We reviewed CDER's files associated with all 15 new molecular entities approved in FY 2001. We obtained the paper copies of key documents for each drug's review process, referred to by FDA as the drug's action package. Each drug's action package includes the reviewer evaluations, correspondences between FDA and the sponsor, and meeting minutes. For these new molecular entities, we also reviewed the documents posted on CDER's website. The CDER posts on its website for each approved drug the approval letter, the label, and the reviewer evaluations.

For these same 15 new molecular entities, we also obtained the receipt dates for all amendments to the application submitted by the sponsor from CDER's decision support system. We entered these dates into Microsoft® Excel for analysis. Our analysis included the number and type of amendments CDER received, and when in the review process CDER received these amendments.

## **Observations of CDER Meetings**

We observed 17 meetings held by CDER that were associated with NDAs. Nine of these meetings were between CDER and sponsors, 7 of which occurred during the investigational new drug phase and 2 of which occurred during the NDA review process. Seven of these meetings were internal CDER meetings during the NDA review process. And, we observed one advisory committee meeting. Many of these meetings occurred during the course of a 2-day observation of a division director of a review division within CDER. We developed a structured meeting observation guide to focus our observations and notes.

## **Analysis of CDER's Data on Advisory Committees**

We obtained data from CDER on advisory committee meetings it held between the calendar years 1997 - 2001 related to an NDA. The FDA can hold advisory committees

to address issues unrelated to a specific NDA. We did not include those meetings in our analysis. Based on this data, we calculated the number of advisory committees per year and estimated the percentage of approved NDAs that had an advisory committee meeting. We used Microsoft® Excel for our analysis.

We estimated the percentage of approved drugs with an advisory committee using a database of all advisory committees associated with an NDA during the calendar years 1997 - 2001. It is possible that a drug that was approved between 1998 and 2001 could have had an advisory committee prior to 1997; therefore, the advisory committee was not included in our analysis. This is most likely to be the case for the year 1998, resulting in the percentage of approved new drugs with an advisory committee being an underestimate. If this is the case, this would not affect our overall conclusion that the percentage of approved new drugs with an advisory committee has declined (see Table 6).

<b>Table 6. Estimated Percentage of Approved Drugs By CDER with an Advisory Committee Meeting</b>				
<b>Calendar Year</b>	<b>Percent of All Approved New Drugs with an Advisory Committee Meeting</b>	<b>Percent of Approved Standard Drugs with an Advisory Committee Meeting</b>	<b>Percent of Approved New Molecular Entities with an Advisory Committee Meeting</b>	<b>Percent of Approved Priority Drugs with an Advisory Committee Meeting</b>
1998	19% (17/90)	3% (2/65)	40% (12/30)	60% (15/25)
1999	24% (20/83)	11% (6/55)	37% (13/25)	50% (14/28)
2000	11% (11/98)	6% (5/78)	19% (5/27)	30% (6/20)
2001	12% (8/66)	9% (5/56)	21% (5/24)	30% (3/10)
Source: OIG Analysis of Data From CDER				

## Interviews with CDER Officials

We conducted 80 interviews with officials from CDER either in person or by telephone. We used a structured interview guide for each interview.

**Office Directors.** We interviewed 17 office directors and the directors of the sub-offices within each of the following offices: the Office of New Drugs, the Office of Clinical Pharmacology and Biopharmaceutics, the Office of New Drug Chemistry, the Office of Drug Safety, and the Office of Medical Policy.

**Division Directors.** We interviewed 27 division directors, including all 15 division directors within the Office of New Drugs. The remaining 12 division directors were from the Office of Clinical Pharmacology and Biopharmaceutics, the Office of New Drug Chemistry, and the Office of Drug Safety.

**Primary and Secondary Reviewers.** We interviewed 18 primary and secondary reviewers. These primary and secondary reviewers represented a variety of review disciplines: 4 clinicians, 3 project managers, 7 clinical pharmacologists and biopharmaceutics, 3 statisticians, and one postmarketing reviewer. Fourteen of these reviewers came from a random sample of 24 primary and secondary reviewers who identified themselves on our survey as willing to be interviewed. The remaining 10 of the 24 individuals either declined, were unavailable, or could not be contacted for an interview. We identified the remaining 4 primary and secondary reviewers for interviews through the course of our inquiry.

**Other FDA officials.** We conducted 20 interviews with other CDER officials, including the director and deputy director of CDER, and individuals from the Review Standards Staff, the Office of Management, the Office of Regulatory Policy, and managers of the project managers within the Office of New Drugs.

## Interviews with Stakeholders

We conducted several in-person and telephone interviews with pharmaceutical representatives and other key stakeholders. We used a structured interview guide for each interview.

**Interviews with pharmaceutical representatives.** We interviewed 9 sponsors. Eight were selected because they were the first to respond to our survey and identified themselves as willing to be interviewed. The remaining sponsor we identified from prior inspection work.

**Interviews with other stakeholders.** We conducted 17 interviews with a variety of stakeholders. Our stakeholders included clinical investigators, scientific and regulatory experts, advisory committee members, representatives from consumer and patient advocacy groups, and representatives from industry organizations.

## Endnotes

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1. More information on PDUFA III can be found on FDA's website at <http://www.fda.gov/oc/pdufa/PDUFA3.html>, accessed June 26, 2002.
2. U.S. Department of Health and Human Services, "PDUFA Reauthorization Good for American Patients," Press Release, June 18, 2002.
3. M. Friedman et. al., "The Safety of Newly Approved Medicines," *Journal of the American Medical Association* 281 (May 12, 1999) 18: 1728-1734.
4. "User Fees Credited with 51% Drop in Average Approval Times Since 1993," *Tufts Center for the Study of Drug Development Impact Reports*, October 2001.
5. There is a provision in FDA's draft guidance on advisory committees to extend the clock for a priority review for 2 months when the sponsor indicates that some of its material for advisory committee members cannot be disclosed to the public due to its proprietary nature. But according to FDA, there has been only one case since the draft guidance was issued where a sponsor indicated that the information was not to be disclosed to the public. In that case, the drug was not a priority review, and as such, the extension did not apply. See "Guidance for Industry: Disclosing Information Provided to Advisory Committees in Connection with Open Advisory Committee Meetings Related to the Testing or Approval of New Drugs and Convened by the Center for Drug Evaluation and Research, Beginning on January 1, 2000." Draft Guidance, December 1999, Food and Drug Administration, U.S. Department of Health and Human Services.
6. The FDA's analysis of turnover does not include losses to other Centers within FDA. It only includes employees that left FDA entirely. The data do not include individuals in the Commission Corps and administrative support positions. The data include reviewers who are biologists, microbiologists, pharmacologists, medical officers, consumer safety staff, chemists, statisticians, and computer specialists.
7. The FDA's analysis includes losses to CDER and includes all employees within the Center. Leaving FDA for a position in private industry was the most common reason for leaving the agency. The next three most common reasons for leaving FDA were retirement, transferring to another agency within the Department of Health and Human Services, and transferring to another Center within FDA.
8. The FDA's data are specifically for end-of-phase 2 meetings for a new molecular entity submitted either as an NDA or a biologic license application. End-of-phase 2 meetings are held prior to the review of the NDA or biologic license application.

9. In some cases, FDA may also approve a patient package insert or a medication guide at the time of approval to be distributed to patients. Patient package inserts are voluntary, except for oral contraceptives, estrogens, and progestational drug products. Medication guides are required by FDA for drugs with serious adverse effects.

10. See 65 *Federal Register*, 246, December 22, 2000, “Requirements on Content and Format of Labeling for Human Prescription Drugs and Biologics; Requirements for Prescription Drug Product Labels; Proposed Rule.” Food and Drug Administration, U.S. Department of Health and Human Services.

11. “Draft Guidance for Industry: Clinical Studies Section of Labeling for Prescription Drugs and Biologics — Content and Format,” July 2001, Food and Drug Administration, U.S. Department of Health and Human Services; and “Draft Guidance for Industry: Content and Format of the Adverse Reactions Section of Labeling for Human Prescription Drugs and Biologics,” June 2000, Food and Drug Administration, U.S. Department of Health and Human Services.

12. The FDA does require a pre-approval safety conference for all new molecular entities. The purpose of this internal meeting is to inform the postmarketing surveillance team of key safety issues related to the drug. These meetings can also be helpful in finalizing any postmarketing requirements FDA may request of the sponsors. “New Drug Applications: Pre-approval Safety Conference,” 6010.1: Manual of Policies and Procedures, Center for Drug Evaluation and Research, Food and Drug Administration, U.S. Department of Health and Human Services.

13. The FDA is not legally required to provide a summary document explaining the overall basis for approval. But, for drugs that are of particular interest, either because they are widely used or because of safety concerns, FDA provides summary information in terms understandable to the general public on its website. Currently, FDA provides this information for 17 drugs, some of which have been withdrawn. See “Major Drug Information Pages” on FDA’s website <http://www.fda.gov/cder/drug/default.htm>, accessed on April 29, 2002.

14. More information on PDUFA III can be found on FDA’s website at <http://www.fda.gov/oc/pdufa/PDUFAGoals.html>, accessed June 26, 2002.

15. U.S. Department of Health and Human Services, “PDUFA Reauthorization Good for American Patients,” Press Release, June 18, 2002.



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