United States Government Accountability Office

GAO

Report to Congressional Requesters

March 2012

PRESCRIPTION DRUGS

FDA Has Met Most Performance Goals for Reviewing Applications

GAO-12-500

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FDA Has Met Most Performance Goals for Reviewing Applications

GAO Accountability * Integrity * Reliability

Highlights

Highlights of GAO-12-500, a report to congressional requesters

Why GAO Did This Study

The Food and Drug Administration (FDA) within the Department of Health and Human Services (HHS) is responsible for overseeing the safety and efficacy of drugs and biologics sold in the United States. New drugs and biologics must be reviewed by FDA before they can be marketed, and the Prescription Drug User Fee Act (PDUFA) authorizes FDA to collect user fees from the pharmaceutical industry to support its review of prescription drug applications, including new drug applications (NDA), biologic license applications (BLA), and efficacy supplements that propose changes to the way approved drugs and biologics are marketed or used. Under each authorization of PDUFA since 1992, FDA committed to performance goals for its drug and biologic reviews.

In preparation for the next PDUFA reauthorization, GAO was asked to examine FDA's drug and biologic review processes. In this report, we (1) examine trends in FDA's NDA and BLA review performance for fiscal years (FY) 2000 through 2010, (2) examine trends in FDA's efficacy supplement review performance for FYs 2000 through 2010, and (3) describe issues stakeholders have raised about the drug and biologic review processes and steps FDA is taking that may address these issues. To do this work, GAO examined FDA drug and biologic review data, reviewed FDA user fee data, interviewed FDA officials, and interviewed two industry groups and five consumer advocacy groups. All of the stakeholder groups participated in at least half of the meetings held by FDA to discuss the reauthorization of the prescription drug user fee program.

View GAO-12-500. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

FDA met most performance goals for priority and standard NDAs and BLAs received from FY 2000 through FY 2010. FDA meets its performance goals by completing its review and issuing an action letter—such as an approval or a response detailing deficiencies that are preventing the application from being approved—for a specified percentage of applications within a designated period of time. FDA designates NDAs and BLAs as either priority—if the product would provide significant therapeutic benefits when compared to available drugs—or standard. FDA met the performance goals for both priority and standard NDAs and BLAs for 10 of the 11 fiscal years GAO examined; FDA did not meet either of the goals for FY 2008. Although FDA had not yet issued an action letter for all of the applications it received in FY 2011 and results are therefore preliminary, FDA was meeting the goals for both priority and standard NDAs and BLAs on which it had taken action. Meanwhile, FDA review time for NDAs and BLAs—the time elapsed between FDA's receipt of an application and issuance of an action letter—increased slightly from FY 2000 through FY 2010. In addition, the percentage of NDAs and BLAs receiving an approval letter at the end of the first review cycle generally increased, although that percentage has decreased for priority NDAs and BLAs since FY 2007.

FDA met most of its performance goals for efficacy supplements from FY 2000 through FY 2010. Specifically, FDA met the performance goals for both priority and standard efficacy supplements for 10 of the 11 fiscal years GAO examined. FDA review time generally increased during the analysis period for both priority and standard efficacy supplements. The percentage of priority efficacy supplements receiving an approval letter at the end of the first review cycle fluctuated from FY 2000 through FY 2010, ranging between 47 percent and 80 percent during this time. The results for standard efficacy supplements showed a steadier increase with the percentage of first-cycle approval letters rising from 43 percent for FY 2000 applications to 69 percent for FY 2010 applications.

The industry groups and consumer advocacy groups we interviewed noted a number of perceived issues related to FDA's review of drug and biologic applications. The most commonly mentioned issues raised by industry and consumer advocacy stakeholder groups were actions or requirements that can increase review times (such as taking more than one cycle to approve applications) and insufficient communication between FDA and stakeholders throughout the review process. Industry stakeholders also noted a perceived lack of predictability and consistency in reviews. Consumer advocacy group stakeholders noted issues related to inadequate assurance of the safety and effectiveness of approved drugs. FDA is taking steps that may address many of these issues, including issuing new guidance, establishing new communication-related performance goals, training staff, and enhancing scientific decision making.

In commenting on a draft of this report, HHS generally agreed with GAO's findings and noted that they reflect what the agency reported for the same time period. HHS also called attention to activities FDA has undertaken to improve the prescription drug review process.

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Abbreviations

BLA	biologic license application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FTE	full-time equivalent
FY	fiscal year
HHS	Department of Health and Human Services
NDA	new drug application
NME	new molecular entity
PDUFA	Prescription Drug User Fee Act
REMS	Risk Evaluation and Mitigation Strategy

GAO
Accountability * Integrity * Reliability

United States Government Accountability Office
Washington, DC 20548

March 30, 2012

The Honorable Richard Burr
Ranking Member
Subcommittee on Children and Families
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Tom Coburn
Ranking Member
Permanent Subcommittee on Investigations
Committee on Homeland Security and Governmental Affairs
United States Senate

The Food and Drug Administration (FDA) within the Department of Health and Human Services (HHS) is responsible for overseeing the safety and efficacy of drugs and biological products sold in the United States.[1] In 1992, Congress passed the Prescription Drug User Fee Act (PDUFA) to provide additional resources for FDA to support the process of reviewing applications for new drugs.[2] PDUFA authorized FDA to collect user fees from the pharmaceutical and biotechnology industries to supplement its annual appropriation for salaries and expenses; these user fees include application fees, annual establishment registration fees, and annual product fees. The prescription drug user fee program has been reauthorized every 5 years since 1992, most recently as part of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which authorizes FDA to collect user fees for fiscal years (FY) 2008 through 2012.[3] User fees have become a larger part of FDA's funding for drug review processes, rising from 26.1 percent of costs in FY 1993—the first year FDA collected user fees for drugs—to 61.5 percent in FY 2010, the most recent year for which data are available. In FY 2010, PDUFA user

[1]Biological products—which include vaccines, blood products, and proteins—are derived from living sources such as humans, animals, and microorganisms, while drugs are chemically synthesized. Unless otherwise indicated, throughout this report we use the term "drug" to refer to both chemically synthesized drugs and therapeutic biological products.

[2]Pub. L. No. 102-571, tit. I, 106 Stat. 4491 (1992).

[3]Pub. L. No. 110-85, tit. I, 121 Stat. 823 (2007). Fees are collected and available for obligation only to the extent and in the amount provided in advance in appropriations acts.

fees collected by FDA—including application, establishment, and product fees—totaled more than $529 million, including over $172 million in application fees.[4]

Application fees are collected for a variety of drug and biologic application types, including new drug applications (NDA), biologic license applications (BLA), and efficacy supplements to approved NDAs and BLAs; the amount of the user fee varies for different types of applications.[5] An NDA is an application to market a new drug—either an innovative drug or a variation of a previously marketed drug. A BLA is an application to market a new biologic. FDA categorizes innovative drugs that have not previously been marketed in any dosage or form as new molecular entities (NMEs); FDA also considers nearly all BLAs to be innovative drugs. An efficacy supplement to an NDA or BLA is submitted to propose changes to the way an approved drug is marketed or used, such as adding or modifying an indication or claim, revising the dose or dose regimen, providing for a new route of administration, or changing the marketing status from prescription to over-the-counter use.

Under each authorization of the prescription drug user fee program, FDA committed to performance goals related to the review of drug applications.[6] FDA meets its performance goals by completing its review and issuing an action letter (i.e., an approval, denial, or complete response) for a specified percentage of applications within a designated period of time.[7] These performance goals, as well as user fee amounts,

[4]For the remainder of this report, we use the term "user fees" to refer to user fees submitted with drug applications such as NDAs, BLAs, and efficacy supplements.

[5]For applications submitted in FY 2012, the fee for the review of an application (e.g., an NDA or BLA) that requires clinical data is $1,841,500. The user fee for applications that do not require clinical data is half this amount ($920,750), as is the fee for efficacy supplements requiring clinical data. Some applications—such as those for orphan designated products to treat rare diseases or conditions—are exempt from user fees. In addition, abbreviated new drug applications, which are applications for the approval of generic drugs, are not subject to user fees.

[6]See Pub. L. No. 110-85, § 101(c), 121 Stat. 823, 825 (2007). The performance goals are identified in letters sent by the Secretary of Health and Human Services to the Chairman of the Senate Committee on Health, Education, Labor, and Pensions and the Chairman of the House Committee on Energy and Commerce, and are published on FDA's website. Each fiscal year, FDA is required to submit a report on its progress in achieving those goals and future plans for meeting them. See 21 U.S.C. § 379h-2(a).

[7]A complete response letter describes any deficiencies that must be corrected in order for an application to be approved.

are negotiated between FDA and industry stakeholders and submitted to congressional committees prior to each reauthorization. FDA's authority to collect user fees for drugs expires on October 1, 2012, and the prescription drug user fee program will need to be reauthorized in order for FDA to continue to collect user fees. In preparation for the reauthorization of the prescription drug user fee program, you requested that we examine FDA's prescription drug review process. In this report, we (1) examine trends in FDA's NDA and BLA review performance for FYs 2000 through 2010, (2) examine trends in FDA's efficacy supplement review performance for FYs 2000 through 2010, and (3) describe the issues stakeholders have raised about the prescription drug review processes and steps FDA is taking that may address these issues. We provide additional details on FDA's NDA and BLA review performance in appendix I and efficacy supplement review performance in appendix II. You also asked us to provide information on the number of full-time equivalent (FTE) staff involved in the prescription drug review process; this information is provided in appendix III.

To determine the trends in FDA's review performance for NDAs, BLAs, and efficacy supplements to approved NDAs and BLAs for FYs 2000 through 2010, we examined data obtained from FDA on the review process for all such applications submitted to FDA in those years. Additionally, we reviewed data on FY 2011 applications in order to provide preliminary performance results for that year. FDA had not yet completed its first review for a majority of the FY 2011 applications at the time we received FDA's data; as these reviews are completed, the preliminary results are likely to change.[8] We reviewed the data for reasonableness and consistency, including screening for missing data, outliers, and obvious errors. We also interviewed FDA officials about steps they take to ensure data reliability. We determined that these data were sufficiently reliable for our purposes. Our analyses focused on the proportion of drug applications in each fiscal year for which FDA met or did not meet the applicable performance goal(s); the FDA review time (i.e., the time counted toward user fee performance goals, from the date of receipt of an application to the date FDA issued an action letter to end the first review cycle); the time to final decision (i.e., the total time between submission of an application and the sponsor's withdrawal of the

[8]Specifically, FDA had completed its first review for only 39 percent of original NDAs and BLAs and 34 percent of original efficacy supplements for FY 2011 at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011.

application or FDA's issuance of an approval or denial action letter in the last completed review cycle); and the percentage of first-cycle decisions that were approvals.[9] We also reviewed user fee data from FDA's annual PDUFA financial reports to Congress for FYs 1993 through 2010 and interviewed FDA staff regarding drug review processes and the data we received from FDA.

To describe the issues stakeholders have raised about the drug review processes and what steps FDA is taking that may address these issues, we interviewed two industry groups representing drug manufacturers and five consumer advocacy groups.[10] All of these groups have participated in at least half of the meetings held by FDA to discuss the reauthorization of the prescription drug user fee program. We performed content analyses of the interviews to determine the most pressing issues based on how often each issue was raised. To describe steps FDA is taking that may address some of these issues, we examined publicly available FDA documents, including the draft agreement between FDA and industry on the user fees and performance goals for FYs 2013 through 2017.

We conducted this performance audit from October 2011 through March 2012 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Drug applications—including NDAs, BLAs, and efficacy supplements—are reviewed primarily by FDA's Center for Drug Evaluation and Research (CDER), with a smaller proportion reviewed by the Center for Biologics Evaluation and Research (CBER).[11] Prior to submission of an

[9]The first review cycle begins when FDA receives an application from a sponsor and ends when FDA issues an action letter. If FDA does not approve the application during the first review cycle, a new review cycle begins if the sponsor resubmits the application to FDA.

[10]When we refer to consumer advocacy groups, we are referring to groups that advocate on behalf of consumers and patients.

[11]FDA also reviews other types of drug applications that are beyond the scope of our work, such as manufacturing supplements that describe changes to production processes, equipment, or facilities used to produce an approved drug.

application, sponsors may choose to seek accelerated approval status if the drug is intended to treat a serious or life-threatening illness (such as cancer) and has the potential to provide meaningful therapeutic benefit to patients over existing treatments.[12] Sponsors of a drug with accelerated approval status may be granted approval on the basis of clinical trials conducted using a surrogate endpoint—such as a laboratory measurement or physical sign—as an indirect or substitute measurement for a clinically meaningful outcome such as survival.[13] According to FDA, the agency generally also speeds its review of drug applications with accelerated approval status by granting them priority review, although priority review can also be granted to an application without accelerated approval status.[14] FDA grants priority review for applications that it expects, if approved, would provide significant therapeutic benefits, compared to available drugs, in the treatment, diagnosis, or prevention of a disease. Applications for which there are no perceived significant therapeutic benefits beyond those for available drugs are granted standard review.

The review process involves evaluating scientific and clinical data in the application submitted by a sponsor to determine whether the drug meets statutory and regulatory standards for safety and effectiveness, manufacturing and controls, and labeling. For example, sponsors must demonstrate "substantial evidence" of effectiveness for the claimed indications of the drug in order for FDA to approve the drug.[15] FDA communicates with sponsors—through telephone conversations, letters, or meetings—issues that arise during its review of an application that may

[12]See 21 C.F.R. §§ 314.500-314.560, 601.40-601.46.

[13]FDA may require that a drug granted accelerated approval undergo postmarketing studies to verify the drug's clinical benefit. Additionally, if FDA concludes that a drug can be safely used only if distribution or use is restricted, FDA will require postmarketing restrictions, such as restricting distribution to certain facilities or physicians with special training or experience. FDA may withdraw approval of a drug granted accelerated approval if postmarketing studies fail to verify clinical benefit or the sponsor fails to adhere to the postmarketing restrictions, or for other reasons.

[14]FDA assesses all applications for priority review eligibility; the sponsor does not need to request priority review. If priority review is granted, the sponsor is notified within 60 days of the start of the review period.

[15]See 21 U.S.C. § 355(d); 42 U.S.C. § 262(j).

prevent FDA from approving the application.[16] In response, sponsors can submit additional information to FDA in the form of amendments to the application. Certain applications are also subject to review by an independent advisory committee.[17] FDA convenes advisory committees to provide independent expertise and technical assistance to help the agency make decisions about drug products. Additionally, FDA might require the sponsor to submit a Risk Evaluation and Mitigation Strategy (REMS) for the drug under review to ensure that the benefits of the drug outweigh its risks.[18]

FDA review time for an original application is calculated as the time elapsed from the date FDA receives the application and associated user fee to the date it issues an action letter; it is calculated using only the first review cycle and therefore does not include any time that may elapse while FDA is waiting for a sponsor to respond to FDA's first-cycle action letter or any review time that elapses during subsequent review cycles.[19] In order to close the review cycle for NDAs, BLAs, and efficacy supplements, FDA must complete its review and issue an approval letter, a denial letter, or a "complete response" letter (i.e., a letter delineating any problems FDA identified in the application that prevented it from

[16]For example, FDA issues a letter to sponsors to inform them of filing review issues that were identified during FDA's initial review of an application. Additionally, approximately midway through its review of an application, FDA provides feedback to sponsors on the general progress and status of the application.

[17]FDA convenes an advisory committee meeting for all applications for NMEs and original BLAs, unless an adequate justification is documented explaining the decision to not hold a meeting. For other applications, an advisory committee may be convened if (1) the clinical trial design used novel clinical or surrogate endpoints, (2) the application raises significant issues regarding the safety or effectiveness of the drug, or (3) the application raises significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease. See 21 U.S.C. § 355(n), (s).

[18]See 21 U.S.C. § 355-1; 42 U.S.C. § 262(a)(2)(D). Examples of elements that may be required as part of a REMS include medication guides, patient package inserts, communication plans to health care providers, prescriber or pharmacy certification, and restrictions on distribution.

[19]If the user fee is not paid within 5 days of receipt of the application, FDA will suspend the review. The review clock is reset to start the first review cycle on the date that the user fee is received.

being approved).[20] The review cycle will also be closed if the application is withdrawn by the sponsor. The date on which one of these actions occurs is used to determine whether the review was completed within the PDUFA goal time frame.[21] If FDA issues a complete response letter, the sponsor may choose to submit a revised application to FDA. These are known as resubmissions and their review is covered under the user fee paid with the original submission. Resubmissions are classified as Class 1 or Class 2 according to the complexity of the information they contain, with Class 2 being the most complex.[22]

Although the prescription drug performance goals have continued to evolve with each reauthorization of the prescription drug user fee program, the goals for NDAs, BLAs, and efficacy supplements have remained fairly stable for recent cohorts—a cohort being comprised of all the submissions of a certain type filed in the same fiscal year (see table 1). For standard NDAs, BLAs, and efficacy supplements, the current goal was phased in until it reached the current level (90 percent of reviews completed within 10 months) in FY 2002. Similarly, the goal for Class 1 NDA and BLA resubmissions was phased in, reaching its current level of 90 percent of reviews completed within 2 months in FY 2001. FDA can extend the review time frame for NDAs, BLAs, or Class 2

[20]According to FDA officials, FDA rarely issues a denial letter. If FDA issues a complete response letter to conclude its review of an application, FDA provides the sponsor an opportunity to meet with reviewing officials to discuss what further steps need to be taken by the sponsor before the application can be approved. FDA may consider a sponsor's failure to take action within 1 year after the issuance of a complete response letter to be a request by the sponsor to withdraw the application, unless the sponsor has requested an extension of time to resubmit the application.

[21]Prior to August 2008, FDA also issued "approvable" and "not approvable" letters. Historically an approvable letter was issued when FDA determined that an application could be approved if the sponsor submitted additional information or agreed to certain conditions, while a not approvable letter indicated that FDA was not able to approve an application due to major deficiencies. Beginning in August 2008, FDA started issuing complete response letters in lieu of approvable and not approvable letters.

[22]Class 1 resubmissions contain only certain information such as draft or final printed labeling, safety or stability updates, or other minor clarifying information. Class 2 resubmissions are those containing any information not specified in the definition of Class 1 resubmission, including any item that would require presentation to an advisory committee.

resubmissions by 3 months if it receives a major amendment to the application from the sponsor within 3 months of the goal date.[23]

Table 1: FDA's NDA, BLA and Efficacy Supplement Performance Goals, FYs 2000 through 2011 Cohorts

	Percentage of reviews to be completed within the PDUFA goal time frame											
Fiscal year cohorts	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Priority NDA, BLA, or efficacy supplement, percentage within 6 months	90	90	90	90	90	90	90	90	90	90	90	90
Standard NDA, BLA, or efficacy supplement, percentage within 10 months[a]	50	70	90	90	90	90	90	90	90	90	90	90
Class 1 NDA or BLA resubmission, percentage within 2 months[b]	70	90	90	90	90	90	90	90	90	90	90	90
Class 2 NDA or BLA resubmission, percentage within 6 months	90	90	90	90	90	90	90	90	90	90	90	90

Source: GAO analysis of FDA data.

Note: A review cohort includes all the drug submissions relating to a particular performance goal that were submitted in a given fiscal year. For example, all NDAs received by FDA from October 1, 2010, to September 30, 2011, make up the NDA review cohort for FY 2011.

[a]For FYs 2000 and 2001, FDA also had a goal to complete 90 percent of these reviews within 12 months.

[b]For FY 2000, FDA also had a goal to complete 90 percent of these reviews within 4 months.

FDA Met Most Performance Goals for Original NDAs and BLAs While FDA Review Time Increased Slightly

FDA met most of its performance goals for priority and standard original NDA and BLA submissions for the FYs 2000 through 2010 cohorts. However, the average FDA review time increased slightly during this period for both priority and standard NDAs and BLAs. The percentage of FDA first-cycle approvals for both priority and standard NDAs and BLAs generally increased from FY 2000 through FY 2010; however, the percentage of first-cycle approvals has decreased for priority NDAs and BLAs since FY 2007.

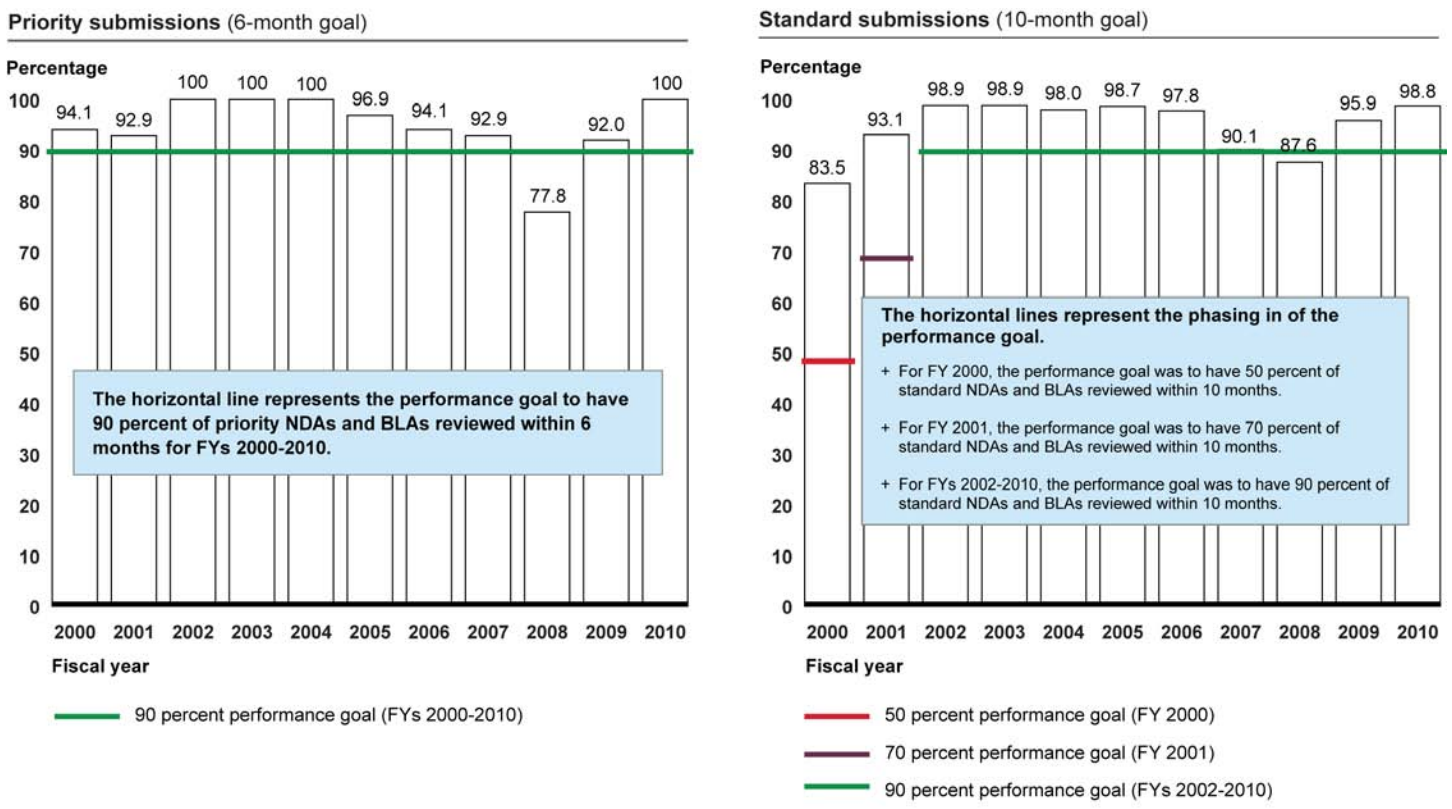
[23]A major amendment is one that contains one or both of the following: (1) a substantial amount of new data or new information not previously submitted to, or reviewed by, FDA (e.g., a major new clinical safety or efficacy study report); or (2) a new analysis or major reanalysis of studies previously submitted for the pending application. A major amendment can be solicited or unsolicited. Prior to FY 2003, FDA did not extend the review time frame for efficacy supplements. Amendments cannot be submitted for Class 1 resubmissions.

FDA Met Most Performance Goals for Original NDAs and BLAs for FYs 2000 through 2010

FDA met most of its performance goals for priority and standard original NDA and BLA submissions during our analysis period by issuing the proportion of action letters specified in the performance goals within the goal time frames. Specifically, for priority original NDAs and BLAs, FDA met the performance goals for 10 of the 11 completed cohorts we examined (see fig. 1). FDA also met the performance goals for 10 of the 11 completed standard NDA and BLA cohorts we examined. However, FDA did not meet the goals (i.e., issue the specified proportion of action letters within the goal time frames) for priority or standard NDAs and BLAs in the FY 2008 cohort. FDA and industry stakeholders we interviewed suggested that the reason FDA did not meet the goals for this cohort was that extra time was required for implementation of REMS requirements, which were introduced as part of the implementation of FDAAA. Although the FY 2011 cohort was still incomplete at the time we received FDA's data, FDA was meeting the goals for both priority and standard original NDAs and BLAs on which it had taken action.[24]

[24]Approximately 32 percent of priority original NDAs and BLAs and 70 percent of standard original NDAs and BLAs received in FY 2011 were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. As a result, it was too soon to tell what the final results for this cohort would be. The percentage of priority and standard original drug submissions reviewed within 6 months and 10 months, respectively, may increase or decrease as those reviews are completed.

Figure 1: Percentage of Priority and Standard Original NDAs and BLAs FDA Reviewed within 6 Months and 10 Months, Respectively, FYs 2000 through 2010



Source: GAO analysis of FDA data.

Notes: A review cohort includes all of the drug submissions relating to a particular performance goal that were submitted in a given fiscal year. Only original NDAs and BLAs that had received an action letter from FDA at the time we received FDA's data were included in this analysis; the data include reviews by CBER and CDER through November 30, 2011. The review cycle for original submissions starts when FDA receives a submission and ends when FDA issues an action letter or the sponsor withdraws the submission.

Priority and standard designations are associated with different lengths of time allotted (6 and 10 months, respectively) for FDA to complete its review of original drug submissions and issue an action letter. If FDA completed its review of a priority submission in 6 months or less, it met the priority goal time frame. If FDA completed its review of a standard submission in 10 months or less, it met the standard goal time frame. Our calculations include extensions of the goal time frame, where applicable. Goal time frames can be extended by 3 months if the sponsor submits a major amendment to the application within 3 months of the goal date.

For FYs 2000 and 2001, FDA also had a goal to complete 90 percent of standard reviews within 12 months.

For the subset of priority NDAs and BLAs that were for innovative drugs, FDA met the performance goals for 9 of the 11 completed cohorts—all cohorts except FYs 2008 and 2009. For the subset of standard NDAs and BLAs that were for innovative drugs, FDA also met the performance goals for 9 of the 11 completed cohorts—all cohorts except FYs 2007 and 2008. For the incomplete FY 2011 cohort, FDA was meeting the goals for the subsets of both priority and standard NDAs and BLAs that were for innovative drugs.

If FDA issues a complete response letter to the sponsor noting deficiencies with the original submission, the sponsor can resubmit the application with the deficiencies addressed. For Class I NDA and BLA resubmissions, FDA met the performance goals for 8 of the 11 completed cohorts we examined.[25] For Class 2 NDA and BLA resubmissions, FDA met the performance goals for 10 of the 11 completed cohorts we examined. Although the FY 2011 cohort was still incomplete at the time we received FDA's data, FDA was meeting the goals for both the Class 1 resubmissions and the Class 2 resubmissions on which it had taken action.

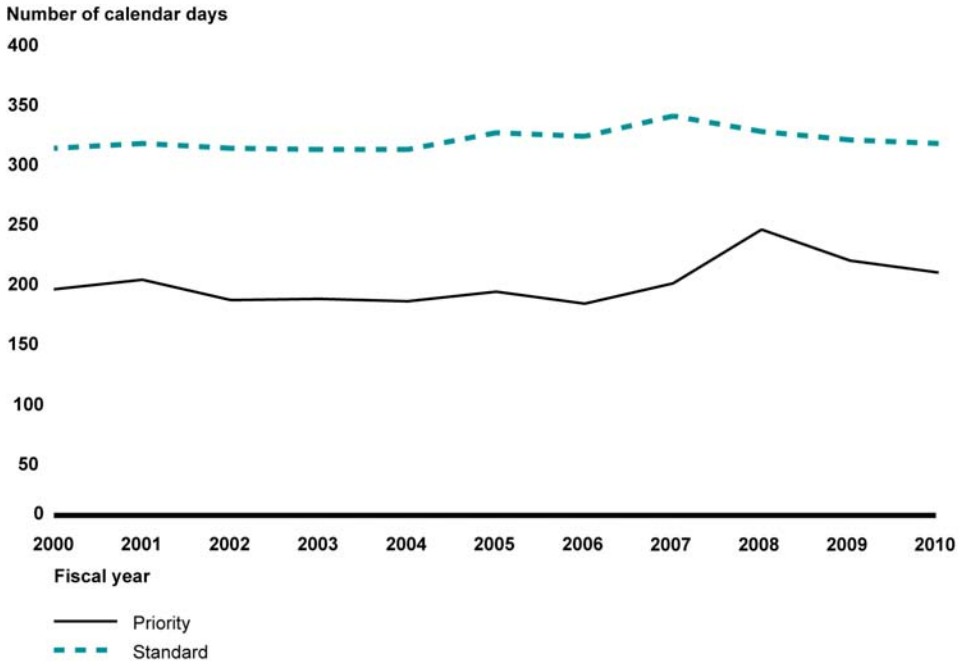
Average FDA Review Time Increased Slightly for Original NDAs and BLAs from FY 2000 through FY 2010

Overall, average FDA review time—the time elapsed from when FDA received a submission until it issued an action letter—increased slightly from FY 2000 through FY 2010 for both priority and standard NDAs and BLAs. There was a larger increase in average review time for both types of applications beginning in FY 2006. However, average review time began decreasing after FY 2007 for standard applications and after FY 2008 for priority applications, bringing the review times back near the FY 2000 levels (see fig. 2). As mentioned previously, FDA and industry stakeholder groups noted the implementation of REMS requirements as a contributing factor to increased review times for the FY 2008 cohort. Although the FY 2011 cohort was still incomplete at the time we received FDA's data, average FDA review time for applications on which FDA had

[25]The performance we report for FDA's review of resubmissions may not match the performance reported in FDA's annual PDUFA performance reports because our analysis was limited to resubmissions made in FYs 2000 through 2011 for original NDAs and BLAs that were also submitted in FYs 2000 through 2011. Resubmissions made in FYs 2000 through 2011 for original NDAs and BLAs submitted prior to FY 2000 were not captured by our analysis.

taken action was 186 days for priority NDAs and BLAs and 308 days for standard NDAs and BLAs.[26]

Figure 2: Average FDA Review Time (in Calendar Days) for Priority and Standard Original NDAs and BLAs, FYs 2000 through 2010



Source: GAO analysis of FDA data.

Note: A review cohort includes all of the drug submissions relating to a particular performance goal that were submitted in a given fiscal year. Only original NDAs and BLAs that had received an action letter from FDA at the time we received FDA's data were included in this analysis; the data include reviews by CBER and CDER through November 30, 2011. The review cycle for original submissions starts when FDA receives a submission and ends when FDA issues an action letter or the sponsor withdraws the submission. Priority and standard designations are associated with different lengths of time allotted (6 and 10 months, respectively) for FDA to complete its review of original drug submissions and issue an action letter.

[26]Approximately 32 percent of priority original NDAs and BLAs and 70 percent of standard original NDAs and BLAs received in FY 2011 were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. As a result, it was too soon to tell what the final results for this cohort would be. The average FDA review time for this cohort may increase or decrease as those reviews are completed.

Trends in average FDA review time for the subset of NDAs and BLAs that were for innovative drugs were similar to trends for all priority or standard NDAs and BLAs. For the subset of priority NDAs and BLAs that were for innovative drugs, average FDA review times were sometimes longer and sometimes shorter than those for all priority NDAs and BLAs; review times for the subset of standard NDAs and BLAs that were for innovative drugs were generally slightly longer than review times for all standard NDAs and BLAs.

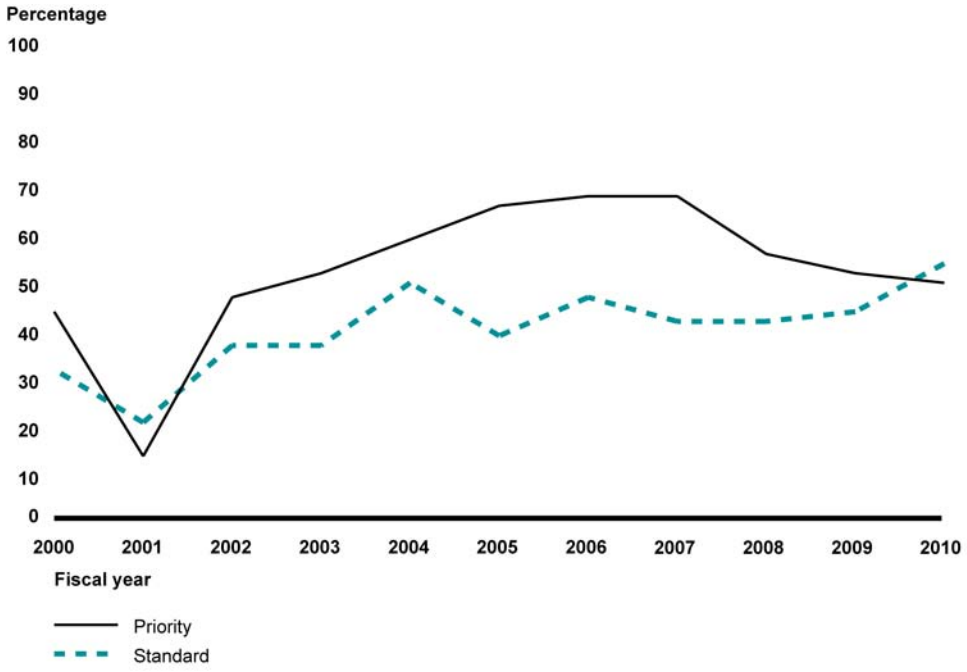
We were unable to calculate the average time to final decision for original NDAs and BLAs—that is, the average time elapsed between submission of an application and the sponsor's withdrawal of the application or FDA's issuance of an approval or denial action letter in the last completed review cycle. Time to final decision includes FDA review time as well as time that elapsed between review cycles while FDA was waiting for the sponsor to resubmit the application. We were unable to complete this calculation because most cohorts were still open for these purposes (i.e., fewer than 90 percent of submissions had received a final action such as approval, denial, or withdrawal). Specifically, for priority NDAs and BLAs, only four cohorts (FYs 2001, 2002, 2005, and 2006) had at least 90 percent of submissions closed, and for standard NDAs and BLAs, only one cohort (FY 2002) had at least 90 percent of submissions closed. (See app. I, table 4 for details.) As a result, there were too few completed cohorts available to calculate the time to final decision in a meaningful way. FDA may opt to consider an application withdrawn (and thus closed) if the sponsor fails to resubmit the application within 1 year after FDA issues a complete response letter. When we examined the open applications using this criterion, we identified 194 open NDAs and BLAs in FYs 2000 through 2010 for which FDA had issued a complete response letter in the most recent review cycle but had not yet received a resubmission from the sponsor. FDA had issued the complete response letter more than 1 year earlier for 162 (84 percent) of these applications.

Percentage of FDA First-Cycle Approvals Generally Increased from FY 2000 through FY 2010 but Decreased for Priority NDAs and BLAs Since FY 2007

The percentage of priority NDAs and BLAs receiving an approval letter at the end of the first review cycle exhibited a sharp 1-year decline from FY 2000 to FY 2001, then increased substantially from FY 2001 through FY 2007, before decreasing again from FY 2007 through FY 2010 (see fig. 3). The percentage of first-cycle approvals for standard NDAs and BLAs showed a similar 1-year decline from FY 2000 to FY 2001, then varied somewhat but generally increased from FY 2002 through FY 2010. Although review of the FY 2011 cohort was incomplete at the time we received FDA's data, 93 percent of the priority NDAs and BLAs that had

received a first-cycle action letter had been approved, as had 42 percent of the standard NDAs and BLAs.[27]

Figure 3: Percentage of Priority and Standard Original NDAs and BLAs Receiving FDA First-Cycle Approvals, FYs 2000 through 2010



Source: GAO analysis of FDA data.

Note: A review cohort includes all of the drug submissions relating to a particular performance goal that were submitted in a given fiscal year. Only original NDAs and BLAs that had received an action letter from FDA at the time we received FDA's data were included in this analysis; the data include reviews by CBER and CDER through November 30, 2011. The review cycle for original submissions starts when FDA receives a submission and ends when FDA issues an action letter or the sponsor withdraws the submission. Priority and standard designations are associated with different lengths of time allotted (6 and 10 months, respectively) for FDA to complete its review of original drug submissions and issue an action letter.

[27]Approximately 32 percent of priority original NDAs and BLAs and 70 percent of standard original NDAs and BLAs received in FY 2011 were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. As a result, it was too soon to tell what the final results for this cohort would be. The percentage of first-cycle approvals for this cohort may increase or decrease as those reviews are completed.

Trends for FYs 2000 through 2010 in the percentage of first-cycle approvals were similar for the subset of NDAs and BLAs that were for innovative drugs when compared to trends for all priority or standard NDAs and BLAs. For the subset of priority NDAs and BLAs for innovative drugs, the percentage of first-cycle approvals was generally higher than for all priority NDAs and BLAs. For standard submissions, the percentage of first-cycle approvals for innovative drugs was generally lower than for all standard NDAs and BLAs; for some cohorts (e.g., FYs 2000, 2004–2006, and 2008) this difference was substantial.

FDA Met Most Performance Goals for Original Efficacy Supplements While FDA Review Time Increased Slightly

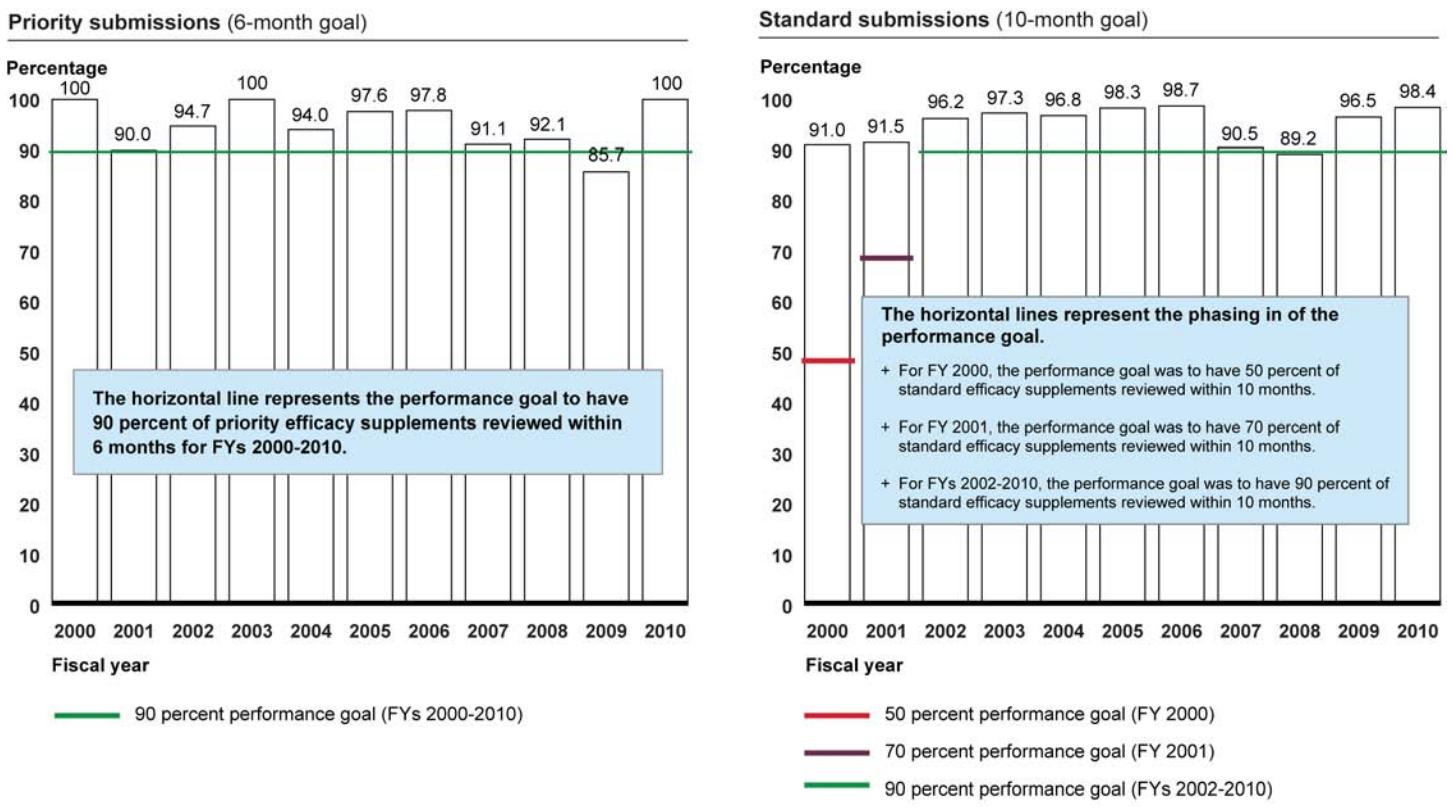
FDA met most of its performance goals for priority and standard original efficacy supplements to approved NDAs and BLAs for the FYs 2000 through 2010 cohorts. However, the average FDA review time generally increased during this period for both priority and standard efficacy supplements. The percentage of FDA first-cycle approvals fluctuated for priority efficacy supplements but generally increased for standard efficacy supplements for the FYs 2000 through 2010 cohorts.

FDA Met Most Performance Goals for Original Efficacy Supplements in FYs 2000 through 2010

FDA met most of its performance goals for efficacy supplements to approved NDAs and BLAs during our analysis period. Specifically, FDA met the performance goals for both priority and standard efficacy supplements for 10 of the 11 completed cohorts we examined (see fig. 4). Although the FY 2011 cohort was still incomplete at the time we received FDA's data, based on efficacy supplements on which it had taken action, FDA was meeting the goal for both priority and standard efficacy supplements.[28]

[28]Approximately 50 percent of priority and 70 percent of standard efficacy supplements received in FY 2011 were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. As a result, it was too soon to tell what the final results for this cohort would be. The percentage of priority and standard efficacy supplements reviewed within 6 and 10 months, respectively, may increase or decrease as those reviews are completed.

Figure 4: Percentage of Priority and Standard Original Efficacy Supplements FDA Reviewed within 6 Months and 10 Months, Respectively, FYs 2000 through 2010



Source: GAO analysis of FDA data.

Notes: A review cohort includes all of the efficacy supplement submissions relating to a particular performance goal that were submitted in a given fiscal year. Only original efficacy supplements that had received an action letter from FDA at the time we received FDA's data were included in this analysis; the data include reviews by CBER and CDER through November 30, 2011. The review cycle for efficacy supplements starts when FDA receives a submission and ends when FDA issues an action letter or the sponsor withdraws the submission.

Priority and standard designations are associated with different lengths of time allotted (6 and 10 months, respectively) for FDA to complete its review of original efficacy supplement submissions and issue an action letter. If FDA completed its review of a priority submission in 6 months or less, it met the priority goal time frame. If FDA completed its review of a standard submission in 10 months or less, it met the standard goal time frame. Our calculations include extensions of the goal time frame, where applicable. Goal time frames can be extended by 3 months if the sponsor submits a major amendment to the application within 3 months of the goal date. Prior to FY 2003, FDA did not extend the goal time frame for efficacy supplement submissions.

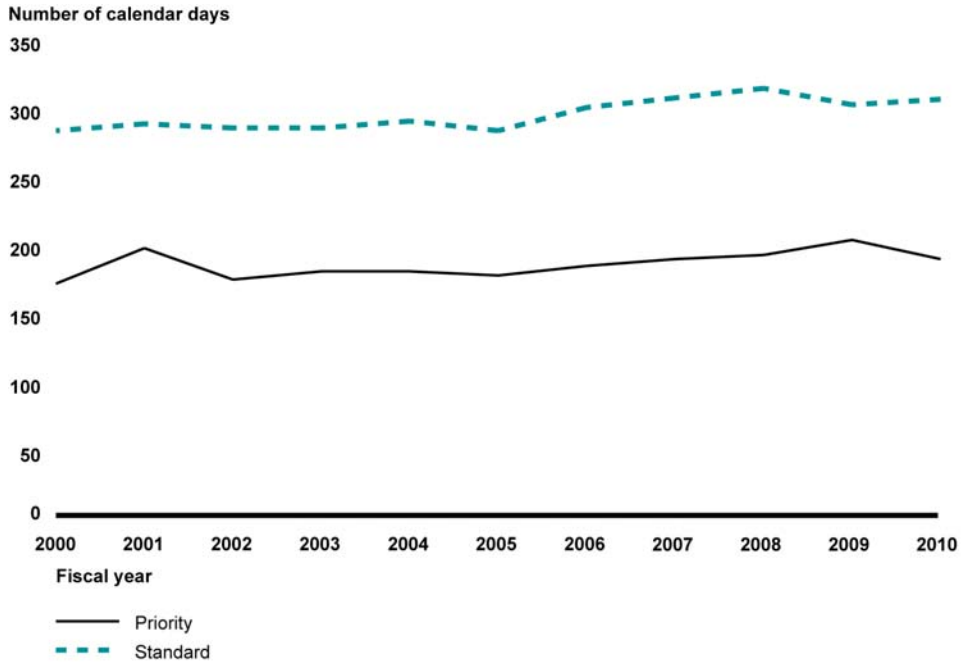
For FYs 2000 through 2001, FDA also had a goal to complete 90 percent of standard reviews within 12 months.

Average FDA Review Time Generally Increased for Original Efficacy Supplements from FYs 2000 through 2010

Average FDA review time generally increased during our analysis period for both priority and standard efficacy supplements. Specifically, average FDA review time for priority efficacy supplements increased from 173 days in the FY 2000 cohort to a peak of 205 days in the FY 2009 cohort and then fell in the FY 2010 cohort to 191 days (see fig. 5). For standard efficacy supplements, average FDA review time rose from 285 days in the FY 2000 cohort to a peak of 316 days in the FY 2008 cohort and then fell in the FY 2010 cohort to 308 days. Although the FY 2011 cohort was still incomplete at the time we received FDA's data, average FDA review time for efficacy supplements on which FDA had taken action was 195 days for priority submissions and 284 days for standard submissions.[29]

[29]Approximately 50 percent of priority and 70 percent of standard efficacy supplements received in FY 2011 were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. As a result, it was too soon to tell what the final results for this cohort would be. The average FDA review time for this cohort may increase or decrease as those reviews are completed.

Figure 5: Average FDA Review Time (in Calendar Days) for Priority and Standard Original Efficacy Supplements, FYs 2000 through 2010



Source: GAO analysis of FDA data.

Note: A review cohort includes all of the efficacy supplement submissions relating to a particular performance goal that were submitted in a given fiscal year. Only original efficacy supplements that had received an action letter from FDA at the time we received FDA's data were included in this analysis; the data include reviews by CBER and CDER through November 30, 2011. The review cycle for efficacy supplements starts when FDA receives a submission and ends when FDA issues an action letter or the sponsor withdraws the submission. Priority and standard designations are associated with different lengths of time allotted (6 and 10 months, respectively) for FDA to complete its review of original efficacy supplement submissions and issue an action letter.

As with NDA and BLA submissions, we were unable to calculate the average time to final decision for efficacy supplements in any meaningful way because there were too few completed cohorts. Specifically, for priority efficacy supplements, only four cohorts (FYs 2000, 2001, 2004, and 2007) had at least 90 percent of submissions closed, and for standard efficacy supplements, only one cohort (FY 2005) had at least 90 percent of submissions closed. (See app. II, table 9 for details.) FDA may opt to consider an application withdrawn (and thus closed) if the sponsor fails to resubmit the application within 1 year after FDA issues a complete response letter. When we examined the open applications using this criterion, we identified 196 open efficacy supplements in FYs 2000 through 2010 for which FDA had issued a complete response letter in the most recent review cycle but had not yet received a resubmission from

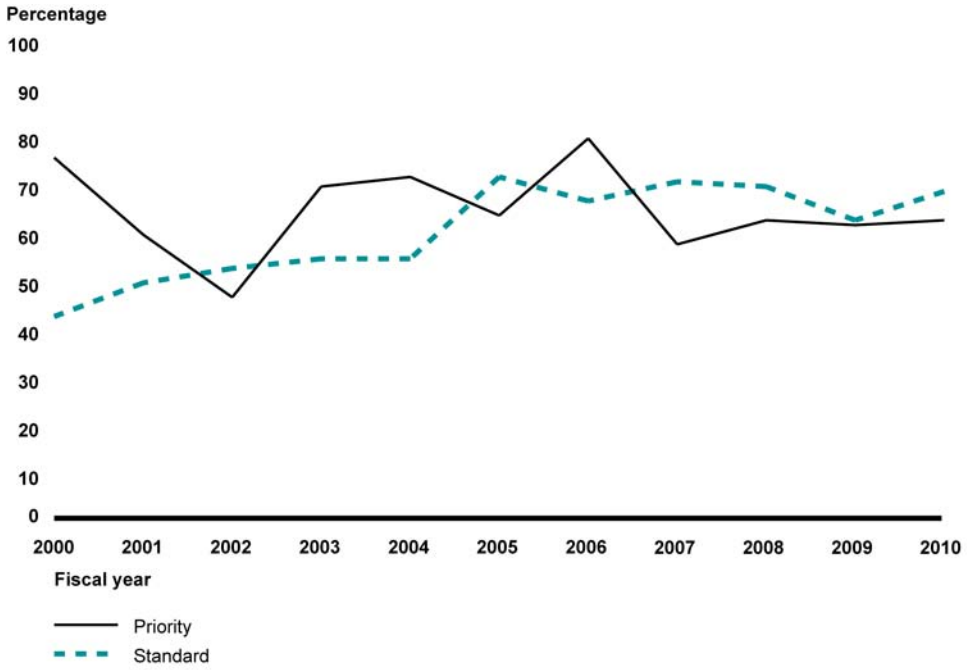
the sponsor. FDA had issued the complete response letter more than 1 year earlier for 168 (86 percent) of these submissions.

Percentage of FDA First-Cycle Approvals Fluctuated for Priority Efficacy Supplements but Generally Increased for Standard Efficacy Supplements from FYs 2000 through 2010

The percentage of priority efficacy supplements receiving an approval decision at the end of the first review cycle fluctuated for FYs 2000 through 2010, ranging between 47 percent and 80 percent during this time (see fig. 6). The results for standard efficacy supplements showed a steadier increase than for priority submissions. Specifically, the percentage of first-cycle approvals rose from 43 percent in the FY 2000 cohort to 69 percent in the FY 2010 cohort. Although the FY 2011 cohort was still incomplete at the time we received FDA's data, 63 percent of first-cycle action letters for standard submissions and 92 percent of first-cycle action letters for priority submissions issued by that time were approvals.[30]

[30]Approximately 50 percent of priority and 70 percent of standard efficacy supplements received in FY 2011 were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. As a result, it was too soon to tell what the final results for this cohort would be. The percentage of first-cycle approvals for this cohort may increase or decrease as those reviews are completed.

Figure 6: Percentage of Priority and Standard Original Efficacy Supplements Receiving FDA First-Cycle Approvals, FYs 2000 through 2010



Source: GAO analysis of FDA data.

Note: A review cohort includes all of the efficacy supplement submissions relating to a particular performance goal that were submitted in a given fiscal year. Only original efficacy supplements that had received an action letter from FDA at the time we received FDA's data were included in this analysis; the data include reviews by CBER and CDER through November 30, 2011. The review cycle for efficacy supplements starts when FDA receives a submission and ends when FDA issues an action letter or the sponsor withdraws the submission. Priority and standard designations are associated with different lengths of time allotted (6 and 10 months, respectively) for FDA to complete its review of original efficacy supplement submissions and issue an action letter.

Stakeholders Noted Issues with the Prescription Drug Review Process and FDA Is Taking Steps That May Address Many of Those Issues

The industry groups and consumer advocacy groups we interviewed noted a number of issues related to FDA's review of prescription drug applications. The most commonly mentioned issues raised by industry and consumer advocacy stakeholder groups were actions or requirements that stakeholders believe can increase review times and insufficient communication between FDA and stakeholders throughout the review process. Industry stakeholders also noted a lack of predictability and consistency in reviews. Consumer advocacy group stakeholders noted issues related to inadequate assurance of the safety and efficacy of approved drugs. FDA is taking steps that may address many of these issues.

Stakeholders Noted Actions or Requirements That They Believe Can Increase Review Times

Most of the seven stakeholder groups we interviewed told us that there are actions and requirements that can lengthen FDA's review process. For example, four of the five consumer advocacy group stakeholders noted that FDA does not require sponsors to submit electronic applications; three of these stakeholders noted that requiring electronic applications could make the review process faster. Additionally, the two industry stakeholders told us that they believe FDA should approve more applications during the first review cycle. We found that an average of 44 percent of all original NDAs and BLAs submitted in FYs 2000 through 2010 were approved during the first review cycle, while 75 percent were ultimately approved.

In addition, the two industry stakeholders that we interviewed raised requirements that can make review times longer, but the consumer advocacy group stakeholders did not agree with these points. For example, both industry stakeholders noted that working out the implementation of REMS requirements introduced in FDAAA slowed FDA's review process. One industry stakeholder stated that discussions about REMS often happened late in the review process, resulting in an increase in review times; another noted that REMS requirements have not been standardized, contributing to longer review times. In contrast, one consumer advocacy group stakeholder that we interviewed suggested that standardized REMS requirements or a "one size fits all" approach would not be meaningful as a risk management strategy. The industry and consumer advocacy group stakeholders also disagreed on another issue that can potentially lengthen the review process—FDA's process for using outside scientific expertise for the review of applications.[31] The two industry stakeholders we interviewed stated that the rules surrounding consultation with an advisory committee—particularly those related to conflicts of interest—can extend the time it takes FDA to complete the review process. In contrast, two of the consumer advocacy group stakeholders we interviewed specifically stated

[31]Both industry stakeholders stated that FDA's ability to consult with advisory committees is inefficient in part due to the associated rules, including the conflict-of-interest provisions in FDAAA and transparency provisions in the Federal Advisory Committee Act. FDAAA placed a cap on the number of conflict-of-interest waivers that FDA can grant annually, and although one stakeholder did not think the number of waivers FDA grants each year approaches this cap, the stakeholder suggested that the very existence of a cap could discourage FDA from granting waivers. See 21 U.S.C. § 379d-1(c). The Federal Advisory Committee Act places a particular emphasis on open meetings, chartering, and public involvement. See 5 U.S.C. app. 2, §§ 9, 10.

that FDA should be concerned with issues of conflict of interest in advisory committees used during the drug review process.

FDA has taken or plans to take several steps that may address issues stakeholders noted can lengthen the review process, including issuing new guidance, commissioning and issuing assessments of the review process, training staff, and establishing programs aimed at helping sponsors. For example, according to the draft agreement with industry for the upcoming prescription drug user fee program reauthorization, FDA would issue guidance on the standards and format for submitting electronic applications and would begin tracking and reporting on the number of electronic applications received.[32] In addition, according to the draft agreement, FDA would publish both an interim and a final assessment of the review process for innovative drugs and then hold public meetings for stakeholders to present their views on the success of the program, including its effect on the efficiency and effectiveness of first-cycle reviews. FDA would also provide training to staff on reviewing applications containing complex scientific issues, which may improve FDA's ability to grant first-cycle approvals where appropriate. In addition, FDA would issue guidance on assessing the effectiveness of REMS for a particular drug and would hold public meetings to explore strategies to standardize REMS, where appropriate. However, we did not identify any examples of steps FDA has taken to address industry stakeholder issues with leveraging outside expertise during the drug review process in any of the recently released strategy, assessment, and guidance documents we reviewed.[33]

[32]In February 2012, FDA issued draft guidance on providing applications in electronic format. See U.S. Department of Health and Human Services, Food and Drug Administration, *Draft Guidance for Industry on Providing Regulatory Submissions in Electronic Format—Standardized Study Data* (Silver Spring, Md.: February 2012).

[33]We considered documents published in 2010 or later to be recently released. In a previous study, GAO found that while FDA faced barriers to recruiting advisory committee candidates without conflicts of interest, the agency may be able to mitigate these barriers by expanding its outreach efforts. See GAO, *FDA Advisory Committees: Process for Recruiting Members and Evaluating Potential Conflicts of Interest*, GAO-08-640 (Washington, D.C.: Sept. 30, 2008).

Stakeholders Cite Insufficient Communication between FDA and Stakeholders throughout the Review Process

Most of the two industry and five consumer advocacy group stakeholders that we interviewed told us that there is insufficient communication between FDA and stakeholders throughout the review process. For example, both of the industry stakeholders noted that FDA does not clearly communicate the regulatory standards that it uses to evaluate applications. In particular, the industry stakeholders noted that the regulatory guidance documents issued by FDA are often out of date or the necessary documents have not yet been developed. Additionally, both industry stakeholders and two consumer advocacy group stakeholders noted that after sponsors submit their applications, insufficient communication from FDA prevents sponsors from learning about deficiencies in their applications early in FDA's review process. According to these four stakeholders, if FDA communicated these deficiencies earlier in the process, sponsors would have more time to address them; this would increase the likelihood of first-cycle approvals. Finally, three consumer advocacy group stakeholders also noted that FDA does not sufficiently seek patient input during reviews. One stakeholder noted that it is important for FDA to incorporate patient perspectives into its reviews of drugs because patients might weigh the benefits and risks of a certain drug differently than FDA reviewers.

FDA has taken or plans to take several steps that may address stakeholders' issues with the frequency and quality of its communications with stakeholders, including conducting a review of its regulations, establishing new review programs and communication-related performance goals, providing additional staff training, and increasing its efforts to incorporate patient input into the review process. FDA is in the process of reviewing its regulations to identify burdensome, unclear, obsolete, ineffective, or inefficient regulations and is soliciting stakeholder input on additional rules that could be improved. In addition, according to the draft agreement with industry, FDA would establish a review model with enhanced communication requirements for innovative drugs, including requirements to hold pre- and late-cycle submission meetings with sponsors as well as to update sponsors following FDA's internal

midcycle review meetings.[34] Additionally, under the draft user fee agreement, FDA would inform sponsors of the planned review timeline and any substantive review issues identified thus far within 74 days of receipt for 90 percent of original NDAs, BLAs, and efficacy supplements. FDA would also issue guidance, develop a dedicated drug development training staff, and provide training on communication for all CDER staff involved in the review of investigational new drugs.[35] Finally, FDA would increase its utilization of patient representatives as consultants to provide patient views early in the product development process and to ensure those perspectives are considered in regulatory discussions. More specifically, FDA would expect to start with a selected set of disease areas and meet with the relevant patient advocacy groups and other interested stakeholders to determine how to incorporate patient perspectives into FDA's decision making.

Industry Stakeholders Report a Lack of Predictability and Consistency in Reviews

The two industry stakeholders that we interviewed also told us that there is a lack of predictability and consistency in FDA's reviews of drug applications. For example, both stakeholders noted that there is sometimes inconsistent application of criteria across review divisions or offices. Further, both industry stakeholders we interviewed noted that FDA lacks a structured benefit-risk framework to refer to when making

[34]At the presubmission meeting, FDA and the sponsor will agree on the content of a complete application, including preliminary discussions on the need for REMS; the agreement and discussion will be summarized at the end of the meeting and will be reflected in the FDA meeting minutes. Following the internal midcycle review meeting, FDA will call the sponsor with an update on the status of the review of its application; this update will include any significant issues identified to date; any information requests; information regarding safety concerns and preliminary thoughts regarding risk management; proposed dates for the late-cycle meeting; updates regarding plans for any potential advisory committee meetings; and other projected milestone dates for the remainder of the review cycle. At the late-cycle meeting, potential topics for discussion include major deficiencies identified to date; issues to be discussed at any planned advisory committee meetings; current assessment of the need for a REMS or other risk management actions; information requests from the review team to the sponsor; and additional data or analyses the sponsor may wish to submit.

[35]Investigational new drugs are drugs permitted by FDA to be tested in humans but that have not been approved for marketing.

decisions, which they believe would improve the predictability of the review process.[36]

FDA has taken or plans to take steps that may address stakeholders' issues with the predictability and consistency of its reviews of drug applications. For example, FDA plans to provide training related to the development, review, and approval of drugs for rare diseases, which may help to improve the consistency of FDA's review of those drugs. In addition, FDA has appointed a Deputy Commissioner for Medical Products to oversee and manage CBER, CDER, and the Center for Devices and Radiological Health (CDRH) in an attempt to improve integration and consistency between the centers. Furthermore, FDA has agreed to create a 5-year plan to develop and implement a structured benefit-risk framework in the review process. FDA will also revise its internal guidance to incorporate a structured benefit-risk framework and then train its review staff on these revisions.

Consumer Advocacy Group Stakeholders Suggest That FDA May Provide Inadequate Assurance of the Safety and Efficacy of Approved Drugs

Three of the five consumer advocacy group stakeholders that we spoke with raised issues about whether FDA is adequately ensuring the safety and efficacy of the drugs it approves for marketing. All three of these stakeholders told us that FDA should place greater priority on safety and efficacy over review speed. In addition, three stakeholders told us that FDA does not gather enough data on long-term drug safety and efficacy through methods such as postmarket surveillance. One stakeholder suggested that FDA should more effectively utilize its Sentinel System for

[36]In mentioning a structured benefit-risk framework, industry stakeholders were referring to an established process for weighing the potential benefits of a new drug against the potential risks it poses.

adverse event reporting.[37] These concerns have also been extensively discussed elsewhere.[38]

FDA has taken or plans to take steps that may address stakeholders' issues with the safety and efficacy of approved drugs, including publishing a regulatory science strategic plan. This document describes various plans FDA has for emphasizing safety and efficacy, such as developing assessment tools for novel therapies, assuring safe and effective medical innovation, and integrating complex data (including postmarket data) to allow for better analyses.[39] FDA has also published a report identifying needs that, if addressed, would enhance scientific decision making in CDER.[40] Some of the needs identified included improving access to postmarket data sources and exploring the feasibility of different postmarket analyses; improving risk assessment and management strategies to reinforce the safe use of drugs; and developing and improving predictive models of safety and efficacy in humans. Finally, in the draft agreement with industry, FDA has committed to conducting both an interim and a final assessment of the strengths, limitations, and appropriate use of the Sentinel System for helping FDA determine the regulatory actions necessary to manage safety issues.

Concluding Observations

FDA met most of the performance goals for the agency to review and issue action letters for original NDA and BLA submissions, Class 1 and Class 2 resubmissions, and original efficacy supplements for the

[37]The Sentinel System is a national electronic system FDA has been developing that will draw on existing automated health care data from multiple sources—such as electronic health record systems, administrative and insurance claims databases, and registries—to monitor the safety of medical products continuously and in real time.

[38]See GAO, *Drug Safety: FDA Has Begun Efforts to Enhance Postmarket Safety, but Additional Actions Are Needed*, GAO-10-68 (Washington, D.C.: Nov. 9, 2009); and *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process*, GAO-06-402 (Washington, D.C.: Mar. 31, 2006). Also see Institute of Medicine of the National Academies, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Washington, D.C.: 2007).

[39]See U.S. Department of Health and Human Services, Food and Drug Administration, *Advancing Regulatory Science at FDA* (Silver Spring, Md.: August 2011).

[40]See U.S. Department of Health and Human Services, Food and Drug Administration, *The CDER Science Prioritization and Review Committee (SPaRC): Identifying CDER's Science and Research Needs Report* (Silver Spring, Md.: July 2011).

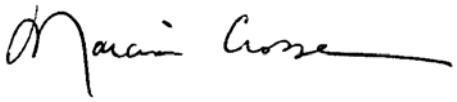
FYs 2000 through 2010 cohorts. FDA review times increased slightly for original NDAs, BLAs, and efficacy supplements during this period while changes in the percentage of first-cycle approvals varied by application type. While FDA has met most of the performance goals we examined, stakeholders we spoke with point to a number of issues that the agency could consider to improve the drug review process; FDA is taking or has agreed to take steps that may address these issues, such as issuing new guidance, establishing new communication-related performance goals, training staff, and enhancing scientific decision making. It is important for the agency to continue monitoring these efforts in order to increase the efficiency and effectiveness of the review process and thereby help ensure that safe and effective drugs are reaching the market in a timely manner.

Agency Comments

HHS reviewed a draft of this report and provided written comments, which are reprinted in appendix IV. HHS generally agreed with our findings and noted that they reflect what the agency reported for the same time period. HHS also called attention to activities FDA has undertaken to improve the prescription drug review process. It highlighted FDA's performance in approving innovative drugs in FY 2011. HHS also noted steps FDA will take to contribute to medical product innovation including expediting the drug development pathway and streamlining and reforming FDA regulations. Finally, HHS discussed enhancements to the drug review program that were included in the proposed recommendations for the 2012 reauthorization of the prescription drug user fee program, such as establishing a new review program for innovative drugs, enhancing benefit-risk assessment, and requiring electronic submissions and standardization of electronic application data to improve efficiency. HHS also provided technical comments, which we incorporated as appropriate.

As agreed with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies of this report to the Secretary of Health and Human Services, the Commissioner of the Food and Drug Administration, and other interested parties. In addition, the report will be available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix V.



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Director, Health Care

Appendix I: FDA NDA and BLA Review Performance for Fiscal Years (FYs) 2000 through 2011

Table 2: FDA Review Performance for Priority Original NDAs and BLAs Including Innovative Drugs, FYs 2000 through 2011

		Fiscal year cohorts											
		2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**[a]
Total number of priority NDA and BLA original submissions	All	34	14	15	23	27	32	34	28	36	25	20	22
	I.D[b]	20	12	11	17	20	21	16	16	18	17	11	14
Number of submissions that were pending (i.e., not complete for PDUFA purposes)	All	0	0	0	0	0	0	0	0	0	0	0	7
	I.D	0	0	0	0	0	0	0	0	0	0	0	4
Number of submissions that were complete for PDUFA purposes	All	34	14	15	23	27	32	34	28	36	25	20	15
	I.D	20	12	11	17	20	21	16	16	18	17	11	10
Number of completed submissions reviewed within 6-month goal[c]	All	32	13	15	23	27	31	32	26	28	23	20	14
	I.D	19	12	11	17	20	20	15	16	14	15	11	9
Percentage of completed submissions reviewed within 6-month goal	All	94	93	100	100	100	97	94	93	78	92	100	93
	I.D	95	100	100	100	100	95	94	100	78	88	100	90
PDUFA goal percentage	All	90	90	90	90	90	90	90	90	90	90	90	90
	I.D	90	90	90	90	90	90	90	90	90	90	90	90
Met PDUFA goal	All	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
	I.D	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes
Average FDA review time (in days) for priority original submissions that were reviewed within goal[d]	All	187	193	184	185	183	188	175	193	197	206	207	172
	I.D	188	195	186	186	185	197	177	191	201	206	210	171
Average FDA review time (in days) for priority original submissions that were not reviewed within goal[d]	All	283	303	—	—	—	254	286	261	405	335	—	382
	I.D	237	—	—	—	—	254	267	—	380	335	—	382
Percentage of first-cycle actions that were:[e]													
Approved	All	44	14	47	52	59	66	68	68	56	52	50	93
	I.D	35	17	55	59	55	71	75	75	61	53	73	100
Complete response[f]	All	56	71	47	43	33	31	29	29	42	48	50	0
	I.D	65	75	36	35	40	29	19	19	33	47	27	0
Withdrawn	All	0	14	7	4	7	3	3	4	3	0	0	7
	I.D	0	8	9	6	5	0	6	6	6	0	0	0
Percentage of final actions that were:[g]													
Approved	All	97	86	93	94	91	93	94	96	97	100	100	93
	I.D	94	92	91	92	93	95	87	94	94	100	100	100
Withdrawn	All	3	14	7	6	9	7	6	4	3	0	0	7
	I.D	6	8	9	8	7	5	13	6	6	0	0	0

Source: GAO analysis of FDA data.

Note: Percentages are rounded to the nearest whole number and may not add to 100 due to rounding.

[a]For the FY 2011 priority NDA/BLA original submission cohort, 7 out of 22 submissions (32 percent) were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. Therefore, values indicated for FY 2011 in the table above may change as these reviews are completed.

[b]"I.D." stands for innovative drugs, a subset of all priority original NDAs and BLAs that includes nearly all BLAs and those NDAs designated as new molecular entities (NMEs).

[c]Our calculations include extensions of the PDUFA goal time frame, where applicable. PDUFA goal time frames can be extended by 3 months if the sponsor submits a major amendment to the application within 3 months of the goal date. For priority NDA/BLA original submissions in FYs 2000 through 2011, 62 out of 311 submissions (20 percent) received PDUFA goal extensions. The percentage was slightly higher for innovative drugs in these cohorts, with 24 percent receiving PDUFA goal extensions.

[d]Average review time for the first review cycle for original submissions. Resubmissions are subject to different PDUFA goal time frames. Dashes (—) indicate cohorts for which no submissions met the criteria.

[e]Includes only those submissions that had received a first-cycle FDA action letter at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011.

[f]Prior to August 2008, FDA also issued "approvable" and "not approvable" letters, which served the same purpose as the complete response letters currently used. We grouped these three types of letters together in our analysis.

[g]Includes only those submissions that had received a final FDA action letter (i.e., approval) in their last completed review cycle or were withdrawn by the sponsor at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011.

Table 3: FDA Review Performance for Standard Original NDAs and BLAs Including Innovative Drugs, FYs 2000 through 2011

		Fiscal year cohorts											
		2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011[a]**
Total number of standard NDA and BLA original submissions	All	97	87	90	89	101	76	89	91	105	123	84	79
	I.D[b]	24	34	21	25	23	22	26	34	32	36	18	24
Number of submissions that were pending (i.e., not complete for PDUFA purposes)	All	0	0	0	0	0	0	0	0	0	0	0	55
	I.D	0	0	0	0	0	0	0	0	0	0	0	19
Number of submissions that were complete for PDUFA purposes	All	97	87	90	89	101	76	89	91	105	123	84	24
	I.D	24	34	21	25	23	22	26	34	32	36	18	5
Number of completed submissions reviewed within 10-month goal[c]	All	81	81	89	88	99	75	87	82	92	118	83	23
	I.D	18	30	20	24	23	21	26	30	26	35	18	5
Percentage of completed submissions reviewed within 10-month goal	All	84	93	99	99	98	99	98	90	88	96	99	96
	I.D	75	88	95	96	100	95	100	88	81	97	100	100
PDUFA goal percentage[d]	All	50	70	90	90	90	90	90	90	90	90	90	90
	I.D	50	70	90	90	90	90	90	90	90	90	90	90
Met PDUFA goal	All	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
	I.D	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Average FDA review time (in days) for standard original submissions that were reviewed within goal[e]	All	297	312	310	300	307	322	320	310	307	309	314	306
	I.D	297	321	308	306	319	327	332	320	308	306	314	303
Average FDA review time (in days) for standard original submissions that were not reviewed within goal[e]	All	386	356	372	1124	354	445	364	599	453	522	405	350
	I.D	411	355	372	1124	—	445	—	477	473	530	—	—
Percentage of first-cycle actions that were:[f]													
Approved	All	32	21	37	37	50	39	47	42	42	44	54	42
	I.D	8	21	33	40	35	18	31	41	25	36	50	20
Complete response[g]	All	59	71	62	58	47	59	49	54	51	53	44	58
	I.D	83	74	67	52	57	82	62	59	66	58	44	80
Withdrawn	All	9	8	1	4	4	1	3	4	7	3	2	0
	I.D	8	6	0	8	9	0	8	0	9	6	6	0

		Fiscal year cohorts											
		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011[a]
Percentage of final actions that were:[h]													
Approved	All	90	89	98	93	95	95	96	94	91	95	96	100
	I.D	90	91	94	89	87	90	89	100	85	92	92	100
Withdrawn	All	10	11	2	7	5	5	4	6	9	5	4	0
	I.D	10	9	6	11	13	10	11	0	15	8	8	0

Source: GAO analysis of FDA data.

Note: Percentages are rounded to the nearest whole number and may not add to 100 due to rounding.

[a]For the FY 2011 standard NDA/BLA original submission cohort, 55 out of 79 submissions (70 percent) were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. As a result, it was too soon to tell what the final results for this cohort would be. Therefore, values indicated for FY 2011 in the table above may change as these reviews are completed.

[b]"I.D." stands for innovative drugs, a subset of all priority original NDAs and BLAs that includes nearly all BLAs and those NDAs designated as new molecular entities (NMEs).

[c]Our calculations include extensions of the PDUFA goal time frame, where applicable. PDUFA goal time frames can be extended for 3 months if the sponsor submits a major amendment to the application within 3 months of the goal date. For standard NDA/BLA original submissions from FYs 2000 through 2011, 168 out of 1,110 submissions (15 percent) received PDUFA goal extensions. The percentage was higher for innovative drugs in these cohorts, with 22 percent receiving PDUFA goal extensions.

[d]In FYs 2000 and 2001, standard original submissions were also subject to a 12-month goal time frame that is not shown in our analysis.

[e]Average review time for the first review cycle for original submissions. Resubmissions are subject to different PDUFA goal time frames. Dashes (—) indicate cohorts for which no submissions met the criteria.

[f]Includes only those submissions that had received a first-cycle FDA action letter at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011.

[g]Prior to August 2008, FDA also issued "approvable" and "not approvable" letters, which served the same purpose as the complete response letters currently used. We grouped these three types of letters together in our analysis.

[h]Includes only those submissions that had received a final FDA action letter (i.e., approval) in their last completed review cycle or were withdrawn by the sponsor at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011.

Table 4: Percentages of Closed and Open NDAs and BLAs, FYs 2000 through 2011

	Fiscal year cohorts											
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Priority NDAs and BLAs												
Percentage of submissions that were closed[a]	85	100	100	78	82	91	94	89	81	76	55	68
Percentage of submissions that were still open[b]	15	0	0	22	18	9	6	11	19	24	45	32
Percentage of submissions that were under FDA review (i.e., pending)	0	0	0	0	0	0	0	4	3	0	20	32
Percentage of submissions for which FDA had issued a complete response and the sponsor had not resubmitted the application	15	0	0	22	18	9	6	7	17	24	25	0
Standard NDAs and BLAs												
Percentage of submissions that were closed[a]	89	83	90	80	85	76	81	71	73	70	65	13
Percentage of submissions that were still open[b]	11	17	10	20	15	24	19	29	27	30	35	87
Percentage of submissions that were under FDA review (i.e., pending)	0	0	0	0	1	0	1	1	6	3	11	72
Percentage of submissions for which FDA had issued a complete response and the sponsor had not resubmitted the application	11	17	10	20	14	24	18	27	21	27	24	15

Source: GAO analysis of FDA data.

Note: Percentages are rounded to the nearest whole number.

[a]We defined a submission as closed if it was approved or withdrawn in the last completed review cycle. Although denial is an action available to FDA officials to close the review of an application, no NDAs or BLAs were denied for FYs 2000 through 2011.

[b]We defined a submission as open if the most recent review cycle was still underway (i.e., pending) or if FDA had issued a complete response letter in the most recent review cycle and the sponsor still had the option of resubmitting the application under the original user fee. Submissions that have received a complete response letter are considered complete for purposes of determining whether FDA met the PDUFA performance goals, but the review is not closed. Prior to August 2008, FDA also issued "approvable" and "not approvable" letters, which served the same purpose as the complete response letters currently used. We grouped these three types of letters together in our analysis.

Table 5: FDA Review Performance for NDA and BLA Resubmissions Including Innovative Drugs, FYs 2000 through 2011

		Fiscal year cohorts											
		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011[a]
Total number of Class 1 NDA and BLA resubmissions[b]	All	3	19	22	22	18	19	20	21	18	16	12	10
	I.D[c]	0	6	11	2	2	2	4	5	4	2	1	2
Number of resubmissions that were pending (i.e., not complete for PDUFA purposes)	All	0	0	0	0	0	0	0	0	0	0	0	2
	I.D	0	0	0	0	0	0	0	0	0	0	0	0
Number of resubmissions that were complete for PDUFA purposes	All	3	19	22	22	18	19	20	21	18	16	12	8
	I.D	0	6	11	2	2	2	4	5	4	2	1	2
Number of completed resubmissions reviewed within 2-month goal	All	3	18	22	21	18	17	20	16	17	13	12	8
	I.D	0	6	11	2	2	2	4	5	4	2	1	2
Percentage of completed resubmissions reviewed within 2-month goal	All	100	95	100	95	100	89	100	76	94	81	100	100
	I.D	—	100	100	100	100	100	100	100	100	100	100	100
PDUFA goal percentage	All	70[d]	90	90	90	90	90	90	90	90	90	90	90
	I.D	70	90	90	90	90	90	90	90	90	90	90	90
Met PDUFA goal	All	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes
	I.D	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total number of Class 2 NDA and BLA resubmissions[b]	All	2	24	35	44	58	32	38	46	34	52	41	53
	I.D	1	14	16	23	22	11	8	22	14	21	11	17
Number of resubmissions that were pending (i.e., not complete for PDUFA purposes)	All	0	0	0	0	0	0	0	0	0	0	0	21
	I.D	0	0	0	0	0	0	0	0	0	0	0	5
Number of resubmissions that were complete for PDUFA purposes	All	2	24	35	44	58	32	38	46	34	52	41	32
	I.D	1	14	16	23	22	11	8	22	14	21	11	12
Number of completed resubmissions reviewed 6-month goal[e]	All	2	24	35	44	57	30	36	43	29	48	39	32
	I.D	1	14	16	23	22	10	8	20	11	20	10	12
Percentage of completed resubmissions reviewed 6-month goal	All	100	100	100	100	98	97	95	93	85	92	95	100
	I.D	100	100	100	100	100	91	100	91	79	95	91	100
PDUFA goal percentage	All	90	90	90	90	90	90	90	90	90	90	90	90
	I.D	90	90	90	90	90	90	90	90	90	90	90	90
Met PDUFA goal	All	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
	I.D	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes

Source: GAO analysis of FDA data.

Note: Percentages are rounded to the nearest whole number.

[a]The FY 2011 cohort was not complete at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. Therefore, values indicated for FY 2011 in the table above may change as these reviews are completed.

[b]Our analysis was limited to resubmissions made in FYs 2000 through 2011 for original NDAs and BLAs that were also submitted in FYs 2000 through 2011. Resubmissions made in FYs 2000 through 2011 for original NDAs and BLAs submitted prior to FY 2000 were not captured by our analysis.

[c]"I.D." stands for innovative drugs, a subset of all priority original NDAs and BLAs that includes nearly all BLAs and those NDAs designated as new molecular entities (NMEs).

[d]In FY 2000, Class 1 resubmissions were also subject to a 4-month goal time frame which is not shown in our analysis.

[e]Our calculations include extensions of the PDUFA goal time frame, where applicable. PDUFA goal time frames for Class 2 resubmissions can be extended for 3 months if the sponsor submits a major amendment to the resubmission within 3 months of the goal date. For Class 2 NDA/BLA resubmissions in these cohorts, 45 out of 463 submissions (9.7 percent) received goal extensions.

Table 6: FDA Review Performance for Oncology Drugs Including Those Granted Accelerated Approval, FYs 2000 through 2011

		Fiscal year cohorts											
		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011[a]
Total number of NDA and BLA original submissions for oncology drugs	All	7	7	6	3	13	10	8	11	8	12	11	15
	A.A.[b]	1	2	2	2	1	3	2	0	1	2	0	1
Number of first-cycle approvals[c]	All	3	4	3	3	8	7	4	6	5	5	6	6
	A.A.	1	1	2	2	1	3	2	—	1	2	—	1
Number of final approvals[d]	All	5	5	4	3	8	8	5	7	7	5	9	6
	A.A.	1	2	2	2	1	3	2	—	1	2	—	1

Source: GAO analysis of FDA data.

[a]For the FY 2011 cohort, 55 out of 79 standard NDA and BLA submissions (70 percent) and 7 out of 22 priority submissions (32 percent) were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. Therefore, values indicated for FY 2011 in the table above may change as these reviews are completed.

[b]"A.A." designates the subset of oncology drug submissions granted accelerated approval status.

[c]Includes only those submissions that had received a first-cycle FDA approval letter at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. Includes tentative approvals (one each in FYs 2005, 2007, and 2009). Dashes (—) indicate cohorts for which no submissions met the criteria.

[d]Includes only those submissions that had received an approval letter in their last completed review cycle at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. Dashes (—) indicate cohorts for which no submissions met the criteria.

Appendix II: FDA Efficacy Supplement Review Performance for Fiscal Years (FYs) 2000 through 2011

Table 7: FDA Review Performance for Priority Efficacy Supplements, FYs 2000 through 2011

	Fiscal year cohorts											
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**[a]
Total number of priority efficacy supplements	21	10	38	37	50	42	45	45	38	42	19	26
Number of submissions that were pending (i.e., not complete for PDUFA purposes)	0	0	0	0	0	0	0	0	0	0	0	13
Number of submissions that were complete for PDUFA purposes	21	10	38	37	50	42	45	45	38	42	19	13
Number of completed submissions reviewed within 6-month goal[b]	21	9	36	37	47	41	44	41	35	36	19	13
Percentage of completed submissions reviewed within 6-month goal	100	90	95	100	94	98	98	91	92	86	100	100
PDUFA goal percentage	90	90	90	90	90	90	90	90	90	90	90	90
Met PDUFA goal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Average FDA review time (in days) for priority efficacy supplements that were reviewed within goal[c]	173	182	169	182	171	176	182	180	189	182	191	195
Average FDA review time (in days) for priority efficacy supplements that were not reviewed within goal[c]	—	347	303	—	356	289	393	309	249	341	—	—
Percentage of first-cycle actions that were:[d]												
Approved	76	60	47	70	72	64	80	58	63	62	63	92
Complete response[e]	14	30	42	30	24	33	20	42	34	33	37	8
Withdrawn	10	10	11	0	4	2	0	0	3	5	0	0
Percentage of final actions that were:[f]												
Approved	89	86	82	100	95	96	100	100	96	90	100	100
Withdrawn	11	14	18	0	5	4	0	0	4	10	0	0

Source: GAO analysis of FDA data.

Note: Percentages are rounded to the nearest whole number and may not add to 100 due to rounding.

[a]For the FY 2011 priority efficacy supplement cohort, 13 out of 26 submissions (50 percent) were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. As a result, it was too soon to tell what the final results for this cohort would be. Therefore, values indicated for FY 2011 in the table above may change as these reviews are completed.

[b]Our calculations include extensions of the PDUFA goal time frame, where applicable. PDUFA goal time frames can be extended for 3 months if the sponsor submits a major amendment to the application within 3 months of the goal date. For priority efficacy supplements in FYs 2000 through 2011, 24 out of 400 submissions (6 percent) received PDUFA goal extensions.

[c]Average review time for the first review cycle for original submissions. Resubmissions are subject to different PDUFA goal time frames. Dashes (—) indicate cohorts for which no submissions met the criteria.

[d]Includes only those submissions that had received a first-cycle FDA action letter at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011.

[e]Prior to August 2008, FDA also issued "approvable" and "not approvable" letters, which served the same purpose as the complete response letters currently used. We grouped these three types of letters together in our analysis.

[f]Includes only those submissions that had received a final FDA approval letter in their last completed review cycle or were withdrawn by the sponsor at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011.

Table 8: FDA Review Performance for Standard Efficacy Supplements, FYs 2000 through 2011

	Fiscal year cohorts											
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008[a]**	**2009[a]**	**2010[a]**	**2011[a]**
Total number of standard efficacy supplements	167	164	131	113	156	116	149	147	112	117	128	107
Number of submissions that were pending (i.e., not complete for PDUFA purposes)	0	0	0	0	0	0	0	0	1	2	1	75
Number of submissions that were complete for PDUFA purposes	167	164	131	113	156	116	149	147	111	115	127	32
Number of completed submissions reviewed within 10-month goal[b]	152	150	126	110	151	114	147	133	99	111	125	32
Percentage of completed submissions reviewed within 10-month goal[c]	91	91	96	97	97	98	99	90	89	97	98	100
PDUFA goal percentage[d]	50	70	90	90	90	90	90	90	90	90	90	90
Met PDUFA goal	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Average FDA review time (in days) for standard efficacy supplements that were reviewed within goal[e]	278	278	282	283	287	283	292	290	297	297	306	284
Average FDA review time (in days) for standard efficacy supplements that were not reviewed within goal[e]	370	395	394	426	463	397	994	499	470	499	399	–
Percentage of first-cycle actions that were:[f]												
Approved	43	50	53	55	55	72	67	71	70	63	69	63
Complete response[g]	51	41	44	45	41	25	28	28	27	35	27	25
Withdrawn	6	9	3	0	4	3	5	1	3	2	5	13
Percentage of final actions that were:[h]												
Approved	87	87	93	100	93	94	93	96	96	96	94	83
Withdrawn	13	13	7	0	7	6	7	4	4	4	6	17

Source: GAO analysis of FDA data.

Note: Percentages are rounded to the nearest whole number and may not add to 100 due to rounding.

[a]For the FYs 2008 through 2011 standard efficacy supplement cohorts, certain submissions were still under review at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011. For FY 2008, 1 out of 112 submissions (less than 1 percent) was still under review. For FY 2009, 2 out of 117 submissions (approximately 2 percent) were still under review. For FY 2010, 1 out of 128 submissions (less than 1 percent) was still under review. For FY 2011, 75 out of 107 submissions (70 percent) were still under review. As a result, it was too soon to tell what the final results for this cohort would be. Therefore, values indicated for these cohorts in the table above may change as these reviews are completed.

[b]Our calculations include extensions of the PDUFA goal time frame, where applicable. PDUFA goal time frames can be extended for 3 months if the sponsor submits a major amendment to the application within 3 months of the goal date. For standard efficacy supplements in FYs 2000 through 2011, 90 out of 1,528 submissions (6 percent) received PDUFA goal extensions.

[c]FYs 2008 through 2011 calculations exclude submissions for which FDA had not yet issued an action letter.

[d]In FYs 2000 and 2001, standard efficacy supplement submissions were also subject to a 12-month goal time frame that is not shown in our analysis.

[e]Average review time for the first review cycle for original submissions. Resubmissions are subject to different PDUFA goal time frames.

[f]Includes only those submissions that had received a first-cycle FDA action letter at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011.

[g]Prior to August 2008, FDA also issued "approvable" and "not approvable" letters, which served the same purpose as the complete response letters currently used. We grouped these three types of letters together in our analysis.

[h]Includes only those submissions that had received a final FDA approval letter in their last completed review cycle or were withdrawn by the sponsor at the time we received FDA's data, which include reviews by CBER and CDER through November 30, 2011.

Table 9: Percentages of Closed and Open Efficacy Supplements, FYs 2000 through 2011

	Fiscal year cohorts											
	2000	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**
Priority efficacy supplements												
Percentage of submissions that were closed[a]	100	100	84	89	92	83	89	93	76	76	74	46
Percentage of submissions that were still open[b]	0	0	16	11	8	17	11	7	24	24	26	54
Percentage of submissions that were under FDA review (i.e., pending)	0	0	0	0	0	0	0	0	0	0	0	50
Percentage of submissions for which FDA had issued a complete response and the sponsor had not resubmitted the application	0	0	16	11	8	17	11	7	24	24	26	4
Standard efficacy supplements												
Percentage of submissions that were closed[a]	83	89	84	86	75	91	82	88	83	80	82	22
Percentage of submissions that were still open[b]	17	11	16	14	25	9	18	12	17	20	18	78
Percentage of submissions that were under FDA review (i.e., pending)	0	0	0	0	0	0	0	0	1	2	1	70
Percentage of submissions for which FDA had issued a complete response and the sponsor had not resubmitted the application	17	11	16	14	25	9	18	12	16	18	17	7

Source: GAO analysis of FDA data.

Note: Percentages may not add to totals due to rounding.

[a]We defined a submission as closed if it was approved or withdrawn in the last completed review cycle. Although denial is an action available to FDA officials to close the review of a submission, no efficacy supplements were denied in FYs 2000 through 2011.

[b]We defined a submission as open if the most recent review cycle was still underway (i.e., pending) or if FDA issued a complete response letter in the most recent review cycle (i.e., the sponsor still had the option of resubmitting the application under the original user fee). Submissions that have received a complete response letter are considered complete for purposes of determining whether FDA met the PDUFA performance goals, but the review is not closed. Prior to August 2008, FDA also issued "approvable" and "not approvable" letters, which served the same purpose as the complete response letters currently used. We grouped these three types of letters together in our analysis.

Appendix III: Full-time Equivalent (FTE) FDA Staff Supporting Prescription Drug User Fee Activities, FYs 2000 through 2010

	Number of FTEs in each fiscal year										
FDA centers and offices	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Center for Drug Evaluation and Research (CDER)											
Office of the Center Director (OCD)	44	38	20	19	13	17	19	22	29	38	49
Office of Regulatory Policy (ORP)[a]	N/A	4	23	26	37	33	45	46	47	49	53
Office of Executive Programs (OEP)[a,b]	N/A	3	39	55	58	58	54	53	57	63	70
Office of Management (OM)	65	66	64	57	46	41	43	45	50	62	75
Office of Communications (OCOMM)[b]	83	87	71	68	72	76	81	53	57	66	72
Office of Compliance (OC)[b]	27	24	30	31	62	39	47	83	101	173	202
Office of Information Technology (OIT/OIM)[c]	99	104	95	87	86	78	88	40	38	40	44
Office of Translational Sciences (OTS)[d]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	147	210	286	323
Office of New Drugs (OND)[e]	705	676	541	593	697	700	725	732	740	858	892
Office of Planning and Informatics (OPI)[c]	N/A	N/A	N/A	N/A	N/A	N/A	N/A	40	48	66	78
Office of Counter-Terrorism and Emergency Coordination (OCTEC)[e]	N/A	N/A	13	33	43	35	39	23	23	24	12
Office of Surveillance & Epidemiology (OSE)[d,e]	N/A	N/A	98	99	118	115	136	113	92	134	167
Office of Medical Policy (OMP)[b]	53	52	54	58	62	47	61	43	46	56	64
Office of Pharmaceutical Science (OPS)[d]	332	320	302	303	379	394	398	299	308	358	376
CDER Total	1,408	1,374	1,350	1,429	1,673	1,633	1,736	1,739	1,846	2,273	2,477[f]
Center for Biologics Evaluation and Research (CBER)											
Center Director's Office, Office of Management (OM), Office of Information Management (OIM) & Office of Communication, Outreach and Development (OCOD)	114	123	124	131	108	106	108	116	128	140	166
Office of Blood Research & Review	38	46	48	53	50	55	50	56	57	67	69
Office of Cellular, Tissue & Gene Therapies	0	0	0	54	69	66	69	75	78	82	92
Office of Vaccines Research & Review	134	136	161	194	201	193	200	217	224	229	238
Office of Therapeutics Research & Review	157	169	189	141	0	0	0	0	0	0	0
Office of Biostatistics & Epidemiology	15	17	22	22	14	16	18	24	30	40	45
Office of Compliance & Biologics Quality	42	42	42	49	36	33	33	34	37	45	44
CBER Total	500	533	586	644	478	469	478	522	554	603	654

	Number of FTEs in each fiscal year										
FDA centers and offices	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**
Office of Regulatory Affairs (ORA)											
ORA Total	180	180	153	147	147	145	142	144	146	194	174
Office of the Commissioner (OC)											
OC Total	257	253	248	212	206	203	218	168	211	283	282
Shared Service (SS)[b,g]											
SS Total	N/A	N/A	N/A	N/A	104	90	117	165	168	173	173
All Centers and Offices Total	**2,345**	**2,340**	**2,337**	**2,432**	**2,608**	**2,540**	**2,691**	**2,738**	**2,925**	**3,526**	**3,760**

Source: GAO analysis of FDA data.

Note: One FTE represents 40 hours of work per week conducted by a federal government employee over the course of 1 year. FTEs do not include contractors and therefore provide a partial measure of staffing resources.

[a]ORP and OEP were created in FY 2001.

[b]In FY 2007, Medical Library staff were transferred from OCOMM to SS, Division of Training staff were transferred from OCOMM to OEP, and the Division of Scientific Investigations was transferred from OMP to OC.

[c]OPI was created in FY 2007 through transfers from OIT; other OIT staff were realigned to OIM.

[d]OTS was created in FY 2007 through transfers from OSE and OPS.

[e]OCTEC and OSE were created in FY 2002 through transfers from OND.

[f]CDER total in FY 2010 includes Commissioner's Fellows.

[g]SS FTEs were not separated from the center FTEs until FY 2004.

Appendix IV: Comments from the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

MAR 16 2012

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) draft report entitled, "PRESCRIPTION DRUGS: FDA Has Met Most Performance Goals for Reviewing Applications"(GAO-12-500).

The Department appreciates the opportunity to review this report before its publication.

Sincerely,

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED, "PRESCRIPTION DRUGS: FDA HAS MET MOST PERFORMANCE GOALS FOR REVIEWING APPLICATIONS" (GAO-12-500)

FDA appreciates the opportunity to comment on GAO's draft report, which recognizes FDA's success in meeting its performance goals over the last 12 years. GAO's findings reflect what the agency has been reporting during the same period and demonstrate that FDA has used the additional resources provided by the prescription drug user fee program as Congress intended: to assure that the agency conducts robust, speedy and efficient reviews of important and cutting-edge prescription drug applications so that the American people may have access to safe and effective therapies that can improve their health and save their lives.

The last decade has been a defining period for FDA as it has enhanced and improved its drug review process and become the world leader in efficient and quality drug reviews. FDA's report, *FY 2011 Innovative Drug Approvals*[1], describes the agency's success in reviewing and approving state of the art therapies for the American people. For example, the report notes that in 2011, FDA approved 35 innovative drugs, many of them groundbreaking. These drugs offer important advances in treatment for hepatitis C, late-stage prostate cancer, lupus, drug resistant skin infections, pneumonia, and other serious and life-threatening diseases. Almost 70% of these drugs received FDA approval before that of any other regulatory agency in the world, including the European Union's (EU) drug regulatory agency. In addition, all but one of these drug approvals met their user fee performance target dates, and most received FDA approval within a single review cycle. In addition, in recent years, the lengths of FDA review times have been demonstrably shorter than those of the EU, with the help of the resources and tools collected under the prescription drug user fee program.

In addition to leading the world in first-time drug approvals, FDA recognizes its critical role in fostering medical innovation. In October 2011, FDA released a report, *Driving Biomedical Innovation: Initiatives for Improving Products for Patients*[2], which describes steps that FDA will take to contribute to medical product innovation, including building the infrastructure to drive and support personalized medicine, expediting the drug development pathway, modernizing its systems for data mining, scientific computing, and information sharing, and streamlining and reforming FDA regulations to promote innovation and access to care.

FDA has further demonstrated its commitment to strengthening the science and performance of the human drug review program through the proposed recommendations for the 2012 reauthorization of the prescription drug user fee program, which was negotiated with regulated industry and forwarded to Congress in January 2012. The proposed recommendations include the following enhancements:

[1] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM278358.pdf

[2] http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm274333.htm

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED, "PRESCRIPTION DRUGS: FDA HAS MET MOST PERFORMANCE GOALS FOR REVIEWING APPLICATIONS" (GAO-12-500)

- A new review program for new molecular entity drug applications and original biological license applications;
- a series of initiatives to further advance regulatory science and expedite drug development, including:
  - methods for meta-analysis (a technique for combining the findings of independent studies to assess the effectiveness of healthcare interventions),
  - biomarkers and pharmacogenomics (to understand how genes affect a person's response to drugs),
  - use of patient-reported outcomes,
  - development of drugs for rare diseases;
- enhancing benefit-risk assessment;
- enhancing and modernizing the FDA drug safety system including:
  - standardizing Risk Evaluation and Mitigation Strategies;
  - using Sentinel (a national, integrated, electronic system for monitoring medical product safety) to evaluate drug safety issues; and
- requiring electronic submissions and standardization of electronic application data to improve the efficiency of human drug reviews.

FDA strives to meet the challenges of the 21st century in its mission to protect the health of the American people by promoting science and innovation. The enactment of the prescription drug user fee program 20 years ago has revolutionized the drug review process and has allowed FDA to keep pace with the ever evolving science and technology that it must master to achieve its public health mission. The timely and seamless reauthorization of this critical program, which expires this year on September 30, will allow FDA to sustain and build on its significant accomplishments to promote the public health through conducting robust and timely drug reviews and advancing regulatory science to drive medical innovation.

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Appendix V: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crossem@gao.gov

Staff Acknowledgments

In addition to the contact named above, Robert Copeland, Assistant Director; Carolyn Fitzgerald; Cathleen Hamann; Karen Howard; Hannah Marston Minter; Lisa Motley; Aubrey Naffis; and Rachel Schulman made key contributions to this report.