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Report to the Ranking Member, Committee on Finance, U.S. Senate

September 2009

NEW DRUG APPROVAL

FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints

GAO-09-866

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Highlights

Highlights of GAO-09-866, a report to the Ranking Member, Committee on Finance, U.S. Senate

Why GAO Did This Study

Before approving a drug, the Food and Drug Administration (FDA) assesses a drug's effectiveness. This assessment may be based on evidence showing that a drug has a positive impact on a surrogate endpoint—a laboratory measure, such as blood pressure—instead of more direct clinical evidence, like preventing strokes. After approval, FDA often requires or requests a drug sponsor to further study the drug. Concerns have been raised about FDA's reliance on surrogate endpoints and its oversight of postmarketing studies. This report provides information on (1) all drug applications approved based on surrogate endpoints in FDA's accelerated approval process, (2) a subset of applications for potentially innovative drugs approved based on surrogate endpoints under FDA's traditional process, and (3) FDA's oversight of postmarketing studies. GAO identified drugs approved based on surrogate endpoints, obtained the status of related postmarketing studies, and reviewed FDA's oversight of a sample of 35 studies it required under its accelerated approval process, selected to include studies which were at varying levels of completion.

What GAO Recommends

GAO recommends that FDA clarify the conditions under which it would utilize its authority to expedite the withdrawal of drugs under its accelerated approval process. FDA disagreed with the need to develop such clarifying guidance. GAO believes doing so would enhance FDA's oversight.

View GAO-09-866 or key components.
For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

What GAO Found

FDA approved 90 applications for drugs based on surrogate endpoints through its accelerated approval process from the creation of the process in 1992 through November 20, 2008, and about two-thirds of postmarketing studies have been closed. FDA created the accelerated approval process to expedite the approval of drugs which are designed to treat serious or life-threatening illnesses and are expected to provide meaningful therapeutic benefits compared to existing treatments. Under this process, 79 of the 90 applications were approved for drugs to treat cancer, HIV/AIDS, and inhalation anthrax. Because of the need to expedite approval, FDA approves drugs under this process based on surrogate endpoints which are not yet proven substitutes for clinical endpoints, but does require that drug sponsors complete postmarketing studies to confirm the drug's clinical benefit. FDA had required drug sponsors to conduct 144 postmarketing confirmatory studies associated with these 90 applications, and as of December 19, 2008, classified 64 percent as closed—meaning that drug sponsors had met FDA's requirements for these studies or FDA determined the studies were no longer needed or feasible. However, several of the remaining studies have been classified by FDA as open for an extended period.

FDA approved 69 applications on the basis of surrogate endpoints for new molecular entities (NME)—potentially innovative drugs containing active chemical substances that have never been approved for marketing in the United States in any form—through its traditional approval process from January 1998 through June 30, 2008. These 69 NME drugs accounted for about one-third of the 204 applications for NME drugs which FDA approved through its traditional process during this period, many for drugs to treat cancer, heart disease, and diabetes. Unlike surrogate endpoints used in the accelerated process, FDA considers those used in the traditional process as valid substitutes for demonstrating the clinical benefit of drugs, and thus does not require sponsors to complete postmarketing confirmatory studies. However, FDA requested that sponsors complete 175 postmarketing studies to obtain other information on many of these NME drugs, and as of February 13, 2009, FDA classified about one-half as closed.

Weaknesses in FDA's monitoring and enforcement process hamper its ability to effectively oversee postmarketing studies. FDA has not routinely been reviewing sponsors' annual submissions on the status of studies in a timely manner. It has little in the way of readily accessible, comprehensive data to monitor studies' progression and does not consider such oversight a priority. FDA is implementing initiatives to improve its oversight, but it is too early to tell if they will be effective. Although FDA has authority to expedite the withdrawal of a drug from the market if a sponsor does not complete a required confirmatory study with due diligence, or if a study fails to confirm a drug's clinical benefit, it has not specified the conditions that would prompt it to do so. It has never exercised its authority, even when such study requirements have gone unfulfilled for nearly 13 years.

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Abbreviations

ASR	annual status report
BLA	Biologic License Application
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act of 1997
HHS	Department of Health and Human Services
NDA	new drug application
NME	new molecular entity
OIG	Office of Inspector General

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United States Government Accountability Office
Washington, DC 20548

September 23, 2009

The Honorable Charles E. Grassley
Ranking Member
Committee on Finance
United States Senate

Dear Senator Grassley:

The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), is the federal agency responsible for ensuring the safety and effectiveness of medical products, including drugs and biological products.[1] Before a new drug can be marketed in the United States, a drug sponsor must demonstrate that it is safe and effective for its intended use, and obtain approval from FDA.[2] Sponsors can demonstrate safety and effectiveness by conducting studies, known as clinical trials, on human volunteers and then submitting the results, as part of an application, to FDA for review.[3] As part of its approval process, FDA reviews the data in the application, including the results of the clinical trials. If FDA determines that the drug's benefits outweigh its risks, it may approve the sponsor's application to market a new drug.

FDA generally prefers that when conducting clinical trials, sponsors demonstrate the effectiveness of a new drug by showing its impact on a clinical endpoint—a direct measure of how a patient feels, functions, or survives. Demonstrating the effectiveness of a new drug, however, can require a sponsor to study the drug on thousands of patients over several

[1]Biological products are products derived from living sources—such as humans, animals, and microorganisms—that are intended for preventing, treating, or curing diseases or conditions. They include vaccines, blood products, and proteins. See 42 U.S.C. § 262(i), 21 C.F.R. § 600.3(h)(2008). For the remainder of this report we use the term "drug" to refer to both therapeutic biological products and chemically synthesized drugs.

[2]Drug sponsors typically are the applicants who submit new drug applications (NDAs) and biological license applications (BLAs) to FDA for review. A drug sponsor may assume responsibility for the marketing of a new drug, including responsibility for complying with applicable laws and regulations.

[3]FDA's approval of an NDA or BLA means a sponsor can market the new drug. Throughout the remainder of this report we refer to FDA's approval of NDAs and BLAs as approval of "drugs".

years, potentially costing hundreds of millions of dollars. As an alternative to demonstrating a drug's effectiveness by its impact on a clinical endpoint, sponsors may submit, and FDA may approve applications based on clinical trials that demonstrate a new drug's impact on a surrogate endpoint—a laboratory measure or physical sign used as a substitute for a clinical endpoint—that reasonably predicts a clinical benefit. For example, demonstrating that a drug can lower blood pressure may be used as a surrogate endpoint to predict whether the drug is effective in preventing strokes. Through the use of surrogate endpoints, a drug sponsor can demonstrate the effect of a new drug on a surrogate endpoint based on smaller and shorter trials than would be required to prove the drug's effectiveness on a clinical endpoint. Unlike establishing clinical effectiveness, however, demonstrating the effect of a new drug on a surrogate endpoint does not always directly prove any benefit to a patient. Thus, reliance on a surrogate endpoint can create uncertainty because a drug's effect on a clinical outcome may not be known until after the drug is approved and further studied in patients.

FDA allows the use of surrogate endpoints in both the accelerated and traditional approval processes. In 1992 FDA established an accelerated approval process to expedite the approval of applications for certain new drugs that are designed to treat serious or life-threatening illnesses and which are expected to provide a meaningful therapeutic benefit over existing therapy.[4] Due to the need to expedite approval of such drugs, under this process, FDA may accept, as a basis for approval, evidence that demonstrates the drug's impact on surrogate endpoints which are reasonably likely to predict clinical benefit, and have not yet been demonstrated to be valid substitutes for clinical endpoints. Because FDA's approval of a drug based on these surrogate endpoints rarely establishes the drug's clinical benefits in relation to a clinical endpoint, FDA has developed additional regulatory requirements when sponsors use surrogate endpoints under the accelerated process. Specifically, when FDA approves a drug based on a surrogate endpoint under the accelerated approval process, FDA requires a sponsor, as a condition of approval, to conduct postmarketing confirmatory studies to validate that a drug's impact on a surrogate endpoint also leads to clinical benefits for patients.

In contrast, under the traditional process—by which FDA reviews most drugs—FDA recognizes the surrogate endpoints as valid substitutes for

[4]21 C.F.R. pt. 314 subpt. H (2008), 21 C.F.R. pt. 601 subpt. E (2008).

clinical endpoints, and thus there are no such postmarketing study requirements. In addition, under both the accelerated and traditional approval processes, FDA may request—and sponsors may agree—to conduct additional postmarketing studies to address other matters that FDA has determined are worthy of further examination.[5]

Regardless of whether a postmarketing study has been required or requested by FDA, sponsors conducting such studies must comply with provisions in the Food and Drug Administration Modernization Act of 1997 (FDAMA) and implementing regulations to report annually to FDA on the status of postmarketing studies.[6] According to FDA's regulations, sponsors must continue to submit these reports each year until FDA notifies the sponsor, in writing, that it has determined that the study has been fulfilled or that the study is either no longer feasible or would no longer provide useful information.[7]

While FDA has long accepted surrogate endpoints to support drug approval, the use of such endpoints can be controversial. Although the use of surrogate endpoints can expedite drug approvals, it can also add uncertainty when the relationship between a surrogate endpoint and clinical benefit or endpoint has not been fully established. Recently, concerns have surfaced about some drugs which FDA approved based on surrogate endpoints. For example, in 2008 FDA approved the drug Avastin to treat breast cancer based on its ability to limit tumor growth; however, studies used to support approval also showed that the drug did not improve overall survival. You asked us to examine FDA's oversight of drugs approved based on surrogate endpoints. In this report we:

1. identify applications FDA has approved based on surrogate endpoints through its accelerated approval process, including the surrogate

[5]Throughout this report we refer to those postmarketing studies which FDA requested and sponsors committed, in writing, to conduct as "requested" postmarketing studies.

[6]See Pub. L. No. 105-115, § 130, 111 Stat. 2296, 2331-2 (codified at 21 U.S.C. § 356b).

[7]21 C.F.R. §§ 314.81(b)(2)(vii), 601.70(a), (b)(2008). The regulations also explain that status reports of postmarketing studies are required for studies that address (1) clinical safety, (2) clinical efficacy, (3) clinical pharmacology, and (4) nonclinical toxicology. Drug sponsors, but not those producing biologics, must also submit annual reports on postmarketing studies that they have agreed to conduct, or that are conducted on their behalf that concern chemistry, manufacturing, controls, or product stability. 21 C.F.R. § 314.81(b)(2)(viii)(2008).

endpoints used for approval, as well as the status of any associated postmarketing studies;

2. identify applications FDA has approved for selected new drugs based on surrogate endpoints in its traditional approval process, including the surrogate endpoints used for approval, as well as the status of any associated postmarketing studies; and

3. evaluate FDA's oversight of postmarketing studies.

To identify the applications for new drugs that FDA has approved on the basis of surrogate endpoints under the accelerated approval process, we obtained information from FDA, which included a list of all such applications the agency approved from June 1992[8] through November 20, 2008 (app. I contains a list of individual drugs, application numbers, and specific surrogate endpoints used for approval through the accelerated approval process). We analyzed this information to determine the number of approvals per year, the endpoints used for approval (e.g., measures of viral load), and the diseases that drugs were approved to treat based on surrogate endpoints.

To identify the number and status of postmarketing studies FDA has required or requested for those drugs approved based on surrogate endpoints under the accelerated approval process, we obtained a list of such studies from FDA. Because FDA may approve multiple applications for the same drug, the same study can be associated with multiple applications;[9] therefore, we utilized a unique numerical identifier assigned by FDA to each study to ensure that we did not count the same study more than once. For those postmarketing studies required under the accelerated approval process, FDA also provided certain key dates related to the progress of these studies, including the dates drug sponsors submitted their final study reports to FDA, and the dates FDA notified sponsors it had approved these reports. We then used this information, which was current as of December 19, 2008, to determine, among other things, the number and percentage of postmarketing studies by status and the average time it took sponsors to fulfill their postmarketing study requirement. To provide the most current information on the status of these studies, FDA

[8]FDA issued final regulations for the accelerated approval process on December 11, 1992, but approved one application under this process, prior to issuing the final regulations. We have included this application in the scope of our review.

[9]For example, if a drug can be taken either as a pill or via injection, FDA may approve a separate application for each route of administration.

had to research electronic and paper files because the information was not readily available in the database FDA uses to track the status of postmarketing studies. To assess the reliability of the information FDA provided, we compared the status and key dates for a sample of studies to the source data contained in FDA's files. We determined the data were sufficiently reliable for the purpose of our review.

Similar to the postmarketing studies FDA required under its accelerated approval process, FDA did not have readily available data on studies it requested, such as certain key dates related to progress of the studies including the dates FDA approved final study reports. Because FDA officials indicated that it would be too time consuming to generate these time line data, as they did for the required studies, they only provided us with status information from their database used to track postmarketing studies. They provided us with data as of January 6, 2009. For these requested postmarketing studies, we also used a unique numerical identifier assigned by FDA for each study to ensure that we did not count the same study more than once. We then identified the number and percentage of studies by status and by the length of time studies have remained open. We could not determine how long it took sponsors to fulfill studies, because the dates FDA determined the studies were fulfilled were not readily available. We did not verify the accuracy of this information. One limitation of using these data was that status information may not be current if FDA had not updated it in a timely manner. However, this represents the best information available and is what FDA uses to track the progress of requested postmarketing studies.

To identify applications for selected new drugs that FDA approved on the basis of surrogate endpoints under the traditional process, we limited our scope to a subset of drugs. Because FDA could not readily identify the extent to which it approves applications based on surrogate endpoints through its traditional process, we reviewed only those applications FDA approved for new molecular entities (NMEs)—potentially innovative drugs containing active chemical substances that have never been approved for marketing in the United States in any form.[10] Although applications for NME drugs represented only about 10 percent of all applications FDA approved during this period, we limited our review to NME drugs because they represent the newest and potentially most innovative drugs. As a

[10]The scope of applications included in this review was limited to NDAs for NMEs. This review does not include any new BLAs.

result, we believe our analyses would capture many of the key concerns related to the use of surrogate endpoints for new drug approval. One limitation of our analysis is that the percentage of NME drugs approved based on surrogate endpoints cannot be projected to the other drugs FDA approved through the traditional process during this period.

Specifically, we reviewed information on all 219 applications for NME drugs that FDA approved from January 1, 1998, through June 30, 2008, and determined the proportion of applications FDA approved that were based on surrogate and clinical endpoints. This time period provided the most recent 10-year approval window at the time of our review. Of the 219 NME drugs, we excluded 15 because they were not approved to treat a specific disease.[11] For the remaining 204 NME drugs, we examined documents summarizing the results of clinical trials for each of them. These documents, accessed from FDA's Web site, included the drugs' original labeling and FDA's original medical reviews.[12] We reviewed these documents and determined whether or not the primary endpoint—the principal measure used to determine whether the drug was effective—for each of the 204 NME drugs was a surrogate or clinical endpoint. We then submitted our analyses to FDA to confirm that we correctly identified the endpoints as surrogate or clinical for each of the 204 applications we reviewed (app. II contains a list of individual drugs, application numbers, and specific surrogate endpoints used for approval through the traditional approval process). After identifying the number of applications for NME drugs in our sample approved on the basis of surrogate endpoints through the traditional approval processes, we determined the number of approvals per year, the specific endpoints used for approval, and the diseases for which drugs were approved.

To identify the number and status of postmarketing studies FDA requested for the approved NME drugs, we obtained a list of such studies from FDA, including information on the status of each study at the time of our review. FDA provided us with data on the status of studies as of February 13, 2009. We then used the same approach for analyzing information on these requested postmarketing studies as we used for those studies requested by

[11]FDA approved 15 NMEs for drugs used to aid in diagnosing diseases or in aiding the absorption of other drugs. Because these 15 were not used to actually treat a disease, we excluded them from our analyses.

[12]We obtained this material from FDA's Web site, www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/.

FDA under the accelerated approval process, subject to the same limitations.

To evaluate FDA's oversight of postmarketing studies, we reviewed relevant laws and regulations, and policy documents describing FDA's program oversight and enforcement authority. We also examined internal control standards, which include the need to establish policies and procedures to help ensure effective and efficient operations.[13] We interviewed FDA officials to identify the oversight activities it engages in to monitor the postmarketing studies it has required or requested sponsors to conduct. We also reviewed the enforcement tools FDA uses or can use to ensure sponsors conduct these studies. To review specific instances of FDA's monitoring and enforcement activities, we selected a judgmental sample of 15 applications approved based on surrogate endpoints under the accelerated program and the 35 postmarketing studies that FDA required drug sponsors to complete for these drugs. These applications were selected to generate a sample that included a variety of drugs and a range of studies at various stages of completion. We provided FDA with a standard series of questions for each of the 35 studies, and requested that FDA's medical reviewers, who are responsible for monitoring these 35 studies, provide specific information on them, including a description of the studies, FDA's efforts to monitor these studies, and applicable enforcement actions taken, if any, to prompt sponsors' compliance (app. III identifies the 15 applications which we selected, and provides the standard series of questions we provided to FDA for each of the 35 postmarketing studies). FDA officials indicated that several individuals were involved in completing the questions provided for each of the 15 applications. FDA staff completed the first half of the questions related to time lines, current statuses, and ASR submissions. The medical reviewers or other staff provided information related to any study completion problems, underlying issues, and monitoring activities. To obtain a better understanding of FDA's oversight of postmarket studies, we reviewed reports issued by HHS's Office of Inspector General (HHS-OIG) and Booz Allen Hamilton, a contractor retained by FDA in 2006 to conduct an independent analysis of the agency's postmarket oversight processes and

[13]For example, under the standards for internal control, information should be recorded and communicated to management and others within an entity who need it and within a time frame that enables them to carry out their internal control and other responsibilities. See GAO, *Standards for Internal Control in the Federal Government*, GAO/AIMD-00-21.3.1 (Washington, D.C.: Nov. 1999) and its supplemental guide, *Internal Control Management and Evaluation Tool*, GAO-01-1008G (Washington, D.C.: Aug. 2001).

procedures. Finally, for certain drugs approved under the accelerated approval process, we obtained annual U.S. sales data from the time the applications for these drugs were approved through December 2008 (app. IV identifies the applications and drugs and the total U.S. sales since approval). As of December 19, 2008, these applications had not been converted to full approval, and more than 5 years had elapsed since they were initially approved. We obtained the annual sales data from IMS Health, a provider of market information to the pharmaceutical and health care industries.

We conducted this performance audit from June 2008 through September 2009 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

FDA's responsibilities for overseeing the safety and effectiveness of drugs begin before a product is brought to market and continue after a drug's approval. Its premarket responsibilities include reviewing a drug sponsor's proposal for conducting clinical trials, as well as reviewing applications. If FDA determines that a drug is safe and effective—that its clinical benefits outweigh its potential health risks—and that other requirements are met, it will approve the application.[14] Once it approves a new drug, FDA is charged with monitoring the safety and effectiveness of the drug, which includes overseeing a sponsor's progress in completing postmarketing studies.

The Benefits and Risks of Surrogate Endpoints in Drug Approval

Reliance on surrogate endpoints to predict clinical benefit can bring treatment benefits to patients years before definitive information on a drug's effect on clinical outcome is available, and at relatively low cost. This is because a drug sponsor may be able to demonstrate the effect of a new drug on a surrogate endpoint based on smaller and shorter trials than would be required to prove the drug's effect on a clinical endpoint. In

[14]FDA will not approve an application if, for example, the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity. 21 U.S.C. § 355(d)(3).

order to further enhance drug development, some have called for their expanded use as a basis for drug approval. For example, FDA's 2004 report on the slowdown of innovative medical therapies calls for the acceptance of new surrogate endpoints to guide drug development.[15] Based on this report, FDA cited the need to clarify the conditions for the use of new surrogate endpoints in the drug approval process. To facilitate this effort, FDA planned to develop an inventory of surrogate endpoints which had been used as the basis for approval of drugs through the traditional and accelerated approval processes.

Despite the potential benefits of using surrogate endpoints, reliance on these endpoints may introduce uncertainty regarding the risks and benefits of a drug, and may lead to the adoption of useless or even harmful therapies.[16] This can arise if the effect on a surrogate endpoint does not accurately predict whether treatments provide benefits to patients, or if the drug has a smaller than expected benefit and a larger than expected adverse effect, which might not be recognized without large-scale, long-term clinical trials. For example, several large trials assessing drugs based on surrogate endpoints found those drugs to be clinically ineffective, and in some cases, identified unexpected adverse effects such as increased rates of death.[17]

FDA Role in the Drug Development and Application Review Process

Once a drug sponsor identifies a promising chemical compound or biologic organism capable of curing or treating diseases, the sponsor may decide to test it on humans. Before doing so, a sponsor must submit the data that have been collected on the compound or organism in prior studies and outline its plans for clinical trials. The clinical trial stage gradually introduces experimental drugs to increasingly larger numbers of patients to determine the drug's safety and efficacy. It is during this stage that a sponsor determines whether it will evaluate a drug's effectiveness using a clinical or surrogate endpoint.

[15]FDA, *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* (March 2004).

[16]R. Temple, *Are Surrogate Markers Adequate to Assess Cardiovascular Disease Drugs?* The Journal of the American Medical Association, August 25, 1999; 282(8):790-795.

[17]For example, see D.S. Echt, P.R. Liebson, L.B. Mitchell, et al, *Mortality and Morbidity in Patients Receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial*, New England Journal of Medicine, 1991; 324:781-788.

Once a drug sponsor completes clinical trials, it may submit an application to FDA for review. The application contains scientific and clinical data intended to demonstrate that the drug is safe and effective for its proposed use. Depending on factors such as the types of disease the drug is designed to treat, whether other effective treatments are available, and whether the sponsor assessed the drug based on a surrogate or clinical endpoint, FDA will review the application under either the accelerated or traditional approval process. If the application is for a drug designed to treat serious or life-threatening illnesses and the drug is expected to provide meaningful therapeutic benefits compared to existing treatments, and the sponsor evaluated the drug's impact on a surrogate endpoint that only reasonably suggested clinical benefit, FDA will review the application under its accelerated approval process. In general, if the sponsor assessed the drug's impact on a clinical endpoint, or a surrogate endpoint that FDA considers to be a valid substitute, FDA will review the application under its traditional approval process.

According to FDA officials, they do not have specific criteria for determining when they will accept a surrogate endpoint as a valid substitute for a clinical endpoint, and such decisions are made on a case-by-case basis. This determination is dependent on factors such as the type of drug being approved and the disease being treated. However, FDA generally considers surrogate endpoints as valid substitutes for clinical endpoints when these endpoints have been shown to accurately predict a clinical benefit over time through definitive studies. For example, FDA considers lowering blood pressure as a valid surrogate endpoint to establish a drug's clinical effectiveness in reducing the risk of stroke.

Regardless of which process FDA uses, the application will be reviewed by one of FDA's medical review divisions, depending on the disease being treated by the drug. The medical review division evaluates data contained in the application to determine whether the drug should be approved. If the medical review division determines the sponsor has demonstrated the drug is safe and effective for its intended use, and has met other applicable requirements, FDA will issue an approval letter. The approval letter outlines any postmarketing studies that FDA has required or requested the sponsor to conduct while the drug is being marketed for sale in the United States—including any associated postmarketing study time frames a sponsor may need to meet.[18] As a condition of approval under its

[18]According to FDA officials, prior to 2001, they did not always establish time frames for completing postmarketing studies.

accelerated approval process, FDA requires that sponsors conduct postmarketing studies known as confirmatory studies. FDA requires sponsors to conduct these postmarketing studies to verify and describe the drug's clinical benefits and thereby resolve any remaining uncertainty regarding the drug's clinical benefit.[19] In addition, FDA may request sponsors to conduct postmarketing studies when it determines that additional information, while not essential for approval, is important in improving the prescribing, use, and quality of a drug or consistency in drug manufacturing. For example, FDA may request sponsors, and sponsors may agree, to continue to evaluate a drug's safety, effectiveness, pharmacology, toxicology, or manufacturing controls. FDA may request these studies under both the accelerated and traditional review processes.

FDA's Oversight of Postmarketing Studies

FDA's oversight of postmarketing studies consists of a variety of monitoring and enforcement activities. After it outlines required and requested studies in the approval letter, FDA is responsible for monitoring sponsors' progress in completing the studies, and taking actions to help ensure studies are completed. A key component of FDA's oversight is the requirement that sponsors of all approved drugs report annually on their progress or status towards completing postmarketing studies. According to the implementing regulations, drug sponsors must report on the status of required and requested postmarketing studies in annual status reports (ASR), which are due within 60 days of the drug application's approval anniversary date.[20] Federal regulations also require ASRs to contain, in

[19]In addition to confirmatory studies, sponsors may be required to conduct postmarketing studies in other instances. For example, under the Pediatric Research Equity Act of 2003 sponsors may be required to study products in children. When a sponsor is required under the act to study its product in pediatric populations, FDA can defer the required studies until after the product is approved in adults. Pub. L. No. 108-55, § 2(a), 117 Stat. 1936 (codified at 21 U.S.C. § 355c(a)(3)(A)(i)(I)). Further, if FDA approves a drug based solely on animal studies, when human efficacy studies are not ethical or feasible, it requires the sponsor to subsequently conduct studies to verify and describe the drug's efficacy and to assess its safety in humans when such studies become feasible and ethical. C.F.R. pts. 314 subpt. I; 601 subpt. H (2008). Finally, the Food and Drug Administration Amendments Act of 2007 (FDAAA) provided FDA with additional authority to require postmarket safety studies in certain instances. Pub. L. No. 110-85, § 901(a), 121 Stat. 823, 922 (codified at 21 U.S.C. § 355(o)).

[20]21 C.F.R. §§ 314.81(b)(2), (b)(2)(vii), 601.70(a)-(c)(2008). The current reporting requirements became effective on April 30, 2001. In 2001, drug sponsors were required to submit their first progress report by October 30 for those postmarketing studies that addressed clinical efficacy, clinical safety, clinical pharmacology, or nonclinical toxicology.

part, information on the description of the required and requested postmarketing studies, along with the schedule for their completion.[21]

FDA has established a goal of reviewing ASRs within 90 days of receipt to confirm the accuracy of the information provided. FDA may use information obtained from the ASRs to update a database that includes information on postmarketing studies. The database, which was designed to allow FDA to track and monitor the status of required and requested postmarketing studies, and identify those studies which are falling behind established time frames, includes information on dates the studies were required or requested in the approval letter, a description of the study, and its status. FDA also makes certain information from this database regarding the status of postmarketing studies available to the public, and is required to report certain information annually in the *Federal Register*.[22]

Based on its review of an ASR, FDA designates a status of either "open" or "closed" for each required and requested postmarketing study every year. FDA further classifies open studies into one of the following five categories:[23]

- **Pending** – Those required and requested studies that have not been initiated, but are not yet delayed. Generally, the first patient has not been enrolled in the study.
- **Ongoing** – Those required and requested studies that are proceeding according to or ahead of any original schedule.
- **Delayed** – Those required and requested studies that are proceeding, but are behind their original schedule.
- **Terminated** – Those required and requested studies that were ended before their actual completion, but the sponsor has not yet submitted a final report to FDA. A postmarketing study may be terminated because the study would no longer provide useful information or the study is no longer feasible. In some instances, there may be another postmarketing study that the drug sponsor must conduct in lieu of the terminated study.

[21]21 C.F.R. §§ 314.81(b)(2)(vii)(*a*)(6), (7); 601.70(b)(6), (7)(2008).

[22]21 U.S.C. 356b(c),(d).

[23]See 21 C.F.R. §§ 314.81(b)(2)(vii)(*a*)(8); 601.70(b)(8)(2008).

- **Submitted** – Those required and requested studies that have been completed—that is, the last patient has finished the protocol—or terminated and a final study report has been submitted to FDA, but FDA has not yet notified the drug sponsor that the study has been fulfilled or released. Drug sponsors are required to continue to annually submit an ASR on the status of its study until FDA provides written confirmation that the obligations have been met.

FDA further classifies "closed" studies into one of the following two categories:

- **Fulfilled** – Those required and requested studies that have been completed and a final study report has been submitted and reviewed by FDA. When FDA completes its review of a study and finds that the postmarketing study has satisfied FDA's request or requirement, the agency will issue a written confirmation to the drug sponsor that it considers the study requested or required in the approval letter to have been fulfilled.

- **Released** – Those required and requested studies that have not been completed and have been found to be no longer needed or feasible. For example, FDA may release a sponsor from the need to compete a study because a new drug has been developed which renders the drug being studied obsolete, thus eliminating the need to conduct the original study.

Once a drug sponsor has completed a postmarketing study, it submits a final study report to FDA for review. FDA's goal is to review the final study report within 12 months of receipt and notify the sponsor whether FDA considers the study closed. If the postmarketing study is a confirmatory study required under the accelerated approval process, the final study report should provide information confirming the drug's clinical benefit. If it provides confirming information, and FDA agrees that the report satisfies the confirmatory study requirements, then FDA converts the drug from accelerated to full approval.[24]

[24]According to FDA, conversion from accelerated to full approval means the sponsor has demonstrated, through clinical testing, that the drug is clinically effective in treating a specific disease or medical condition.

FDA's oversight of postmarketing studies may be aided by enforcement tools, including administrative action letters and expedited withdrawal procedures of a drug from the market, in certain cases.[25] If a sponsor fails to submit or is late in submitting an ASR, or if FDA determines a sponsor is not making adequate progress in completing a required or requested study, FDA may issue an administrative action letter—commonly referred to by FDA as "Dunner" letters. FDA uses these letters to remind sponsors about their need to meet federal requirements related to either submission of ASRs or completing a required or requested study. Also, under the accelerated approval regulations, FDA may initiate procedures to withdraw a drug from the market through an expedited process if required postmarketing studies to confirm and verify a drug's clinical benefit are not performed with due diligence.[26] In contrast, FDA does not require that drug sponsors complete requested postmarketing studies, regardless of whether a drug has been approved under the accelerated or traditional process. Such studies are typically related to safety, effectiveness, pharmacology, toxicology, or manufacturing controls.

FDA Has Approved Many Applications Based on Surrogate Endpoints through Its Accelerated Approval Process and about Two-Thirds of Postmarketing Studies Have Been Closed

FDA has approved 90 applications based on surrogate endpoints under its accelerated approval process since the process was established in 1992. During this period, FDA required or requested sponsors to conduct over 450 postmarketing studies associated with the approval of applications for these drugs, and the majority of these studies have been classified by FDA as closed—meaning that drug sponsors had met FDA's requirements for these studies or FDA determined the studies were no longer needed or feasible. However, several have been classified by FDA as open for an extended period of time.

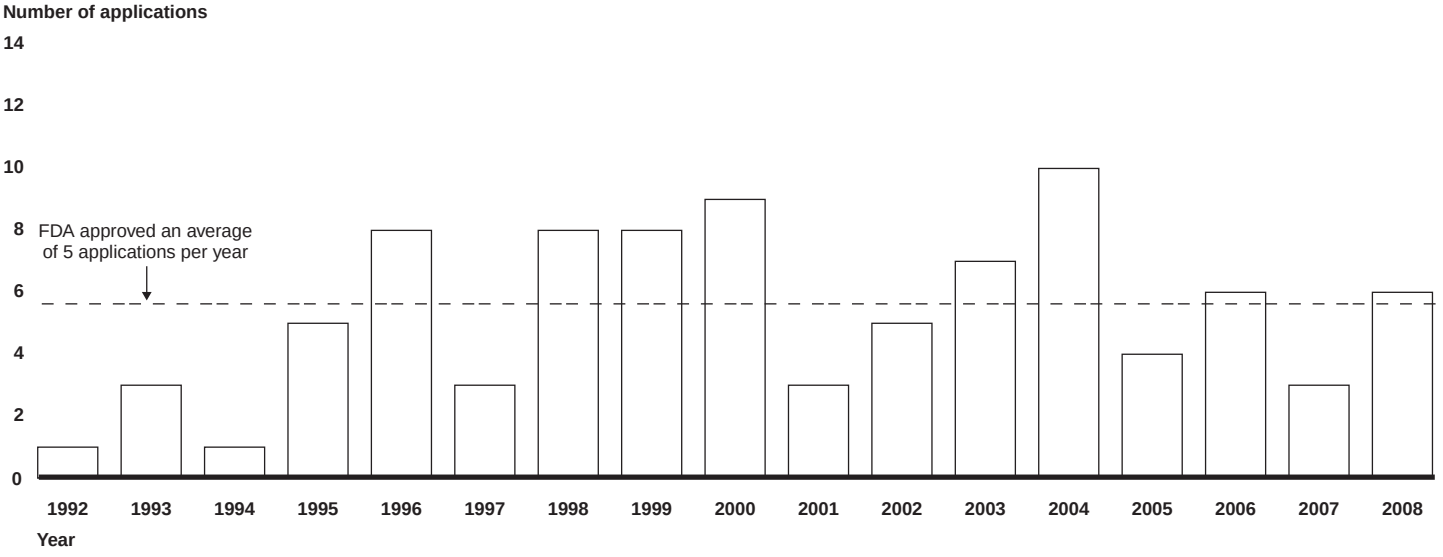
[25]In 2007, FDAAA provided FDA with authority to assess civil monetary penalties against those who have not conducted required postmarketing studies under the accelerated approval process. Pub. L. No. 110-85, §§ 901(a), 902(b) (codified at 21 U.S.C. §§ 333(f)(4), 355(p)). As of July 2009, FDA officials indicated they have never used this new authority.

[26]21 C.F.R §§ 314.530(a)(2), 601.43(a)(2)(2008).

FDA Approved 90 Applications Based on Surrogate Endpoints under the Accelerated Approval Process, the Majority for Drugs to Treat Cancer and HIV/AIDS

From June 19, 1992, through November 20, 2008, FDA approved a total of 90 applications based on surrogate endpoints, or an average of 5 per year. FDA approved these applications for a total of 64 different drugs.[27] Over this period, there was variability in the number of applications FDA approved annually based on surrogate endpoints. For example, in 1992 and 1994, FDA approved 1 application based on surrogate endpoints under the accelerated approval process, while in 2004 it approved 10 applications (see fig. 1).

Figure 1: Applications Approved Using Surrogate Endpoints under FDA's Accelerated Approval Process, June 19, 1992–November 20, 2008



Source: GAO analysis of FDA data.

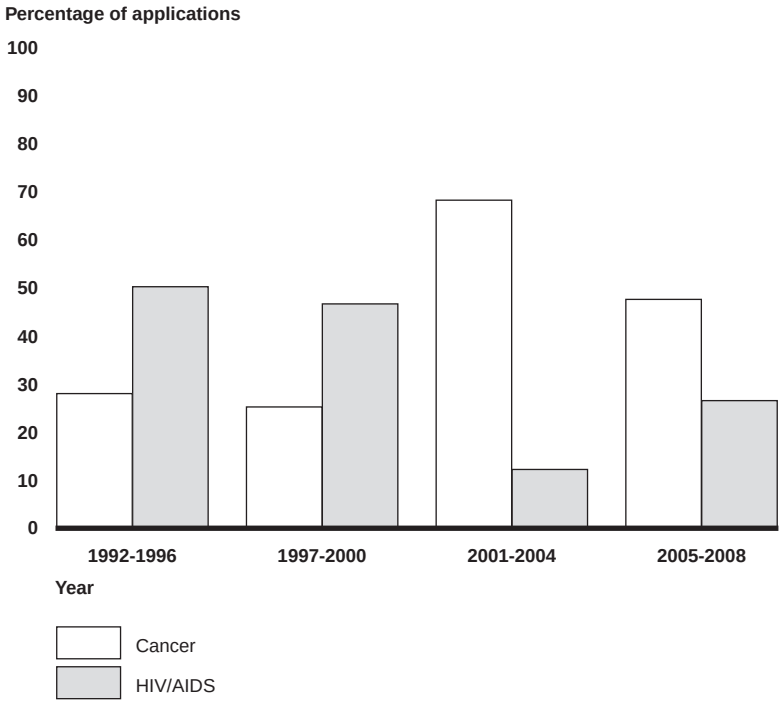
Almost all—79 of the 90 applications—were for drugs to treat three diseases. Specifically, 38 of the applications were for drugs to treat cancer, 30 were for drugs to treat HIV/AIDS, and 11 were for drugs to treat inhalation anthrax. The remaining 11 applications were for drugs to treat a variety of other diseases (app. I contains a list of individual drugs,

[27]In several instances FDA approved multiple applications for the same drug through the accelerated approval process. Thus FDA approved a smaller number of drugs than applications. For example, in some cases a drug had several routes of administration (e.g., tablet, intravenous solution, oral suspension), and FDA approved a separate application for each.

application numbers, and specific surrogate endpoints used for approval through the accelerated approval process).

Since FDA began using the accelerated process in 1992, there has been a general shift in approvals based on surrogate endpoints from applications for HIV/AIDS drugs to applications for cancer drugs. In the first 9 years of the accelerated approval process, from 1992 through 2000, applications for drugs to treat HIV/AIDS made up 48 percent of the approvals, while applications for drugs to treat cancer made up 26 percent of these applications. Conversely, from 2001 through 2008, applications for drugs to treat cancer made up over half—59 percent—of the applications approved, while drugs to treat HIV/AIDS accounted for only 18 percent of approved applications (see fig. 2).

Figure 2: Percentage of Approved Applications Granted Accelerated Approval for Cancer and HIV/AIDS Drugs, June 19, 1992–November 20, 2008



Source: GAO analysis of FDA data.

Consistent with the types of applications approved under the accelerated process, the specific surrogate endpoints most frequently used to obtain approval were those used to demonstrate the effectiveness of cancer and HIV/AIDS drugs. Specifically, FDA approved,

- 38 applications for cancer drugs based on how the drugs impacted tumors, as measured by various tumor assessment surrogate endpoints such as response rate (e.g., tumor shrinkage), length of time until the cancer spread, or length of time until the drug no longer worked;
- 30 applications for HIV/AIDS drugs based on the drugs' ability to lower the viral load of HIV in the blood stream, as measured by the drugs' impact on the surrogate endpoint HIV-RNA; and
- the remaining 22 applications for drugs to treat other diseases—including inhalation anthrax and various bacterial infections—based on a variety of surrogate endpoints (see table 1).

Table 1: Summary of Surrogate Endpoints for Accelerated Application Approvals, from June 19, 1992–November 20, 2008

Disease	Surrogate endpoint(s) used for approval	Number of applications
Cancer	• Tumor assessment • Response rate • Disease-free survival • Progression-free survival • Time to treatment failure • Cytogenic and/or hemotologic response as measured in marrow or blood • Other	38
HIV/AIDS	• Viral load (HIV-RNA) • CD4 count • p24 antigen existence • Other	30
Inhalation anthrax	• Drug exposure in monkeys compared to human plasma concentrations • Serum CIPRO concentrations • Other	11
Other diseases	• Various	11
	Total	**90**

Source: GAO analysis of FDA data.

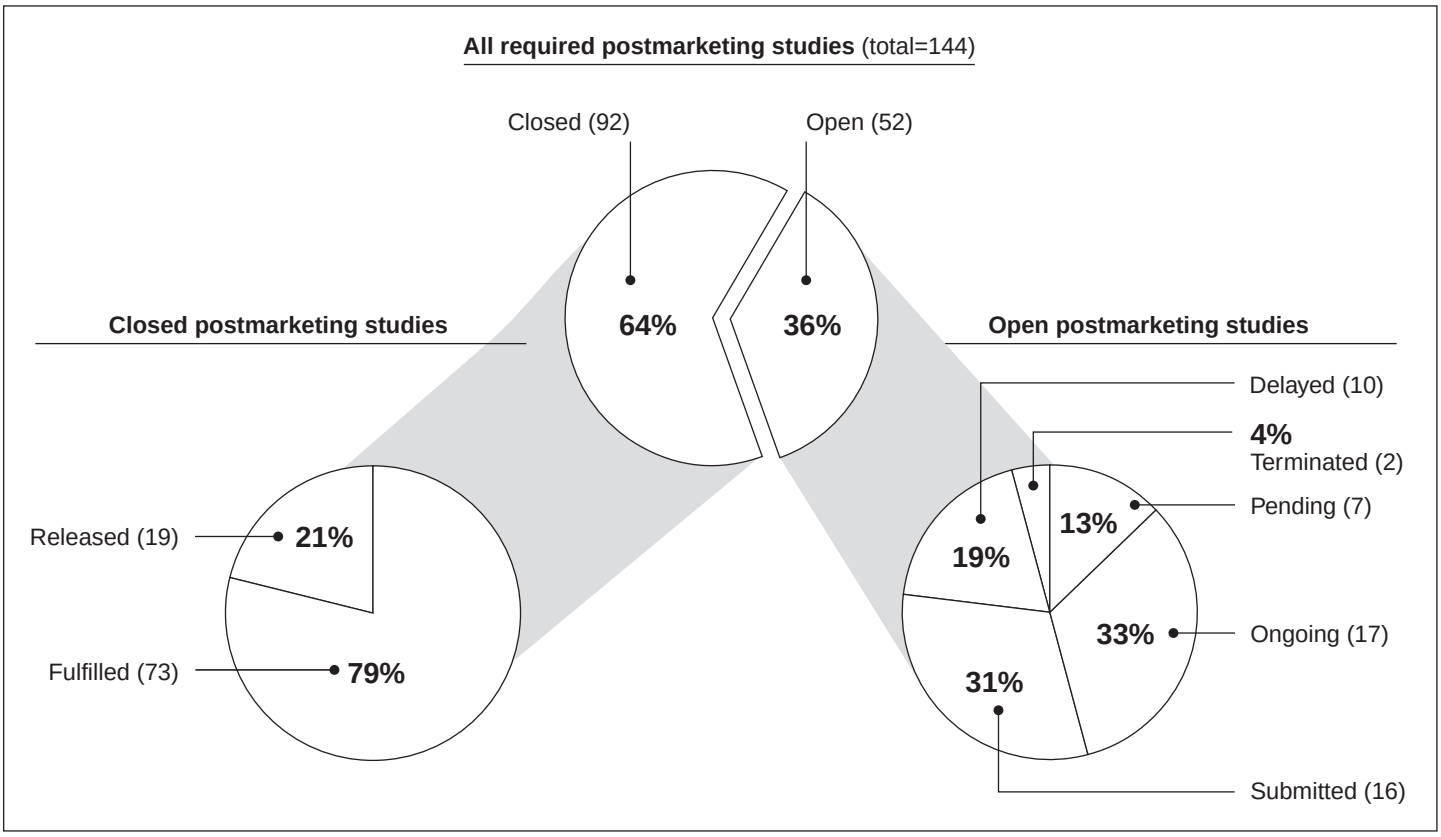
FDA Required 144 Confirmatory Postmarketing Studies under the Accelerated Process, and About Two-Thirds Have Been Closed

From June 1992 through November 20, 2008, FDA required drug sponsors to conduct 144 postmarketing confirmatory studies associated with drugs approved based on surrogate endpoints under the accelerated approval process. Consistent with the types of drugs FDA approved under the process, FDA required the majority of these studies—119 or 79 percent—for drugs approved to treat cancer or HIV/AIDS. Specifically, FDA required 82 studies for drugs to treat cancer, and another 37 studies for drugs to treat HIV/AIDS. The remaining studies were for drugs to treat a variety of other diseases.

At the time of our review, we found FDA had classified 92, or 64 percent, of the 144 required studies as closed—meaning that drug sponsors had met FDA's requirements for these studies or FDA determined the studies were no longer needed or feasible. In contrast, FDA had classified 52 of the 144 studies, or 36 percent, as open, and that sponsors had made varying levels of progress in completing them (see fig. 3).[28]

[28]Two of these open studies are for the drug Levaquin, which was approved to treat the effects of inhalation anthrax. According to FDA officials, these studies will remain in the pending status indefinitely, because the sponsor cannot, for ethical reasons, test the medication on humans unless there is an anthrax attack or other widespread exposure.

Figure 3: Status of Postmarketing Studies FDA Required under Its Accelerated Approval Process, June 19, 1992–November 20, 2008



Source: GAO analysis of FDA data.

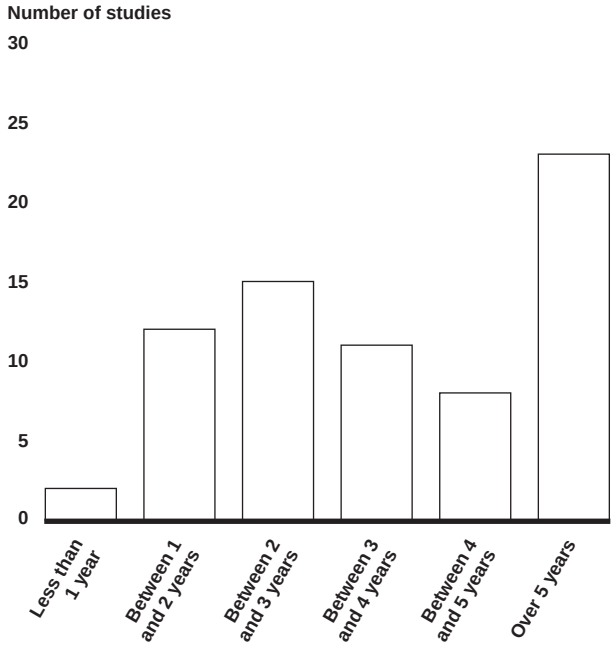
Note: Status as of December 19, 2008.

Of the 92 closed studies, sponsors had fulfilled requirements for 73 of them. This means that sponsors had completed these studies and submitted them to FDA, and upon review, FDA determined sponsors had fulfilled their study requirements. There were an additional 19 studies which FDA classified as released, meaning it had released the sponsors from the study requirements because it determined the studies were either no longer feasible or would no longer provide useful information.

Based on our analyses of the 71 fulfilled studies, we found that in general, sponsors were able to fulfill about two-thirds of their study requirements in less than 5 years, with time frames ranging from 7 months to more than

12 years. In contrast, nearly one-third, or 23, of these studies took over 5 years to fulfill (see fig. 4).[29]

Figure 4: Elapsed Time from Drug Approval to Fulfillment for Postmarketing Studies Required under the Accelerated Approval Process, June 19, 1992–November 20, 2008



Source: GAO analysis of FDA data.

Note: Status as of December 19, 2008.

The amount of time needed to fulfill study requirements was generally longer for those studies involving drugs to treat cancer. Specifically, 61 percent of the postmarketing studies that took over 5 years (14 of 23) were studies for drugs to treat cancer. Conversely, only 9 percent of studies which took over 5 years (2 of 23), were studies for drugs to treat HIV/AIDS. According to FDA officials, the greater length of time needed to fulfill required confirmatory studies for drugs to treat cancer has resulted from the approach generally used to approve many cancer drugs under the

[29]We determined the time to fulfill a study by measuring the amount of time that elapsed from the date the study was required in the approval letter to the date FDA determined the study was fulfilled. FDA was unable to provide the fulfillment dates for 2 of the 73 fulfilled studies; therefore the total number of studies used in fig. 4 is 71.

accelerated process. In particular, most of the cancer drugs gained accelerated approval based on single arm clinical trials,[30] which studied these drugs' impacts in small numbers of patients with resistant tumors. According to FDA officials, this approach has been used to approve drugs targeting resistant tumors because these patients have no other effective therapy and it would be too difficult and time consuming for sponsors to conduct more in-depth randomized control studies.[31] Because patients need access to these drugs as soon as possible, FDA deemed this approach sufficient for accelerated approval. However, in order to establish clinical benefits of the drugs through the required confirmatory postmarketing studies, the sponsors needed to conduct randomized control trials comparing the drugs to either a placebo or another drug(s). To do this, sponsors must design and conduct new randomly controlled clinical trials and recruit new patients, many of whom may be reluctant to sign up for a clinical trial when an approved drug is already on the market. In contrast, according to FDA officials, it is typically easier for a sponsor to complete a required confirmatory study for HIV/AIDS drugs because sponsors may simply continue the study which led to the original accelerated approval of the drug and do not have to design new studies to fulfill the postmarketing study requirements. For example, sponsors typically obtain accelerated approval for HIV/AIDS drugs based on a 24-week randomized clinical trial, and to meet the confirmatory study requirement they continue the same study for an additional 24 weeks, using the same patients and the same endpoints.

The 52 studies FDA classified as open covered a variety of statuses, and thus were at varying levels of completion. Specifically, 7 were pending and had not yet begun, 10 were delayed and thus behind the sponsor's original schedule, and 17 were ongoing, and thus on or ahead of schedule. Additionally, 2 were terminated, meaning the sponsor had stopped the study, but had not submitted results to FDA. The remaining 16 had been submitted by the sponsor to FDA, and were awaiting FDA's review. Based on our analyses of these 52 open studies, we found the majority—approximately 65 percent—were for drugs approved to treat cancer. In

[30]In a single arm trial there is one treatment group of patients who all take the drug being studied; there is not a separate group of patients taking another drug or a placebo for comparison. According to FDA, single arm trials can provide an accurate assessment of tumor response in patients with highly resistant tumors.

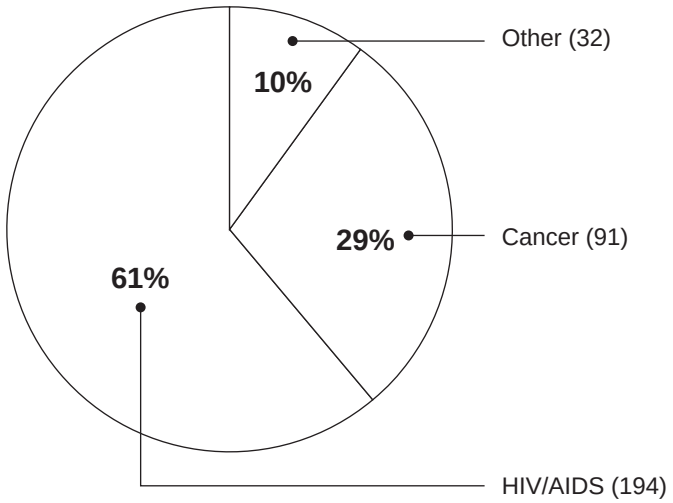
[31]A randomized control trial is a study in which participants are randomly assigned to a group taking the drug under study, a placebo, or a comparison drug. FDA considers a randomized control trial as the most reliable type of trial.

contrast, only 6 percent of the open studies were for drugs approved to treat HIV/AIDS. Based on information provided to us by FDA, we determined that the average age of the 52 open studies was just over 4 years and the majority—37 of the 52 studies, or 71 percent—had been required since 2004. However, we found that 15 studies had been open for more than 5 years, including several open for more than 8 years. For example, on May 17, 2000, FDA approved an application for the drug Mylotarg to treat certain patients with acute myeloid leukemia based on its ability to control cancer in blood cells. As a condition of accelerated approval FDA required the drug sponsor to conduct one confirmatory study, and as of December 19, 2008, more than 8 years later, the study was ongoing, with an anticipated completion date of October 2014.

FDA Requested over 300 Postmarketing Studies under the Accelerated Process, and About Two-Thirds Have been Closed

In addition to the 144 confirmatory studies FDA required from June 1992 through November 20, 2008, FDA also requested—and sponsors agreed to conduct—317 other postmarketing studies associated with drugs approved through the accelerated process based on surrogate endpoints. FDA requested the majority of these studies—90 percent—for drugs approved to treat HIV/AIDS and cancer. Specifically, FDA requested 194 studies for drugs to treat HIV/AIDS, and another 91 studies for drugs to treat cancer. FDA requested the remaining studies for drugs to treat a variety of other diseases (see fig. 5).

Figure 5: Percentage of Postmarketing Studies Requested under the Accelerated Approval Process by Disease, June 19, 1992–November 20, 2008



Source: GAO analysis of FDA data.

Based on the status FDA assigned each study at the time of our review, FDA had classified 203 of the 317 requested studies, or 64 percent, as closed, meaning that drug sponsors had satisfied FDA's request for these studies or FDA determined the studies were no longer needed or feasible.[32] Additionally, we found that FDA had classified 114, or 36 percent, as open, and sponsors had made varying levels of progress in completing them (see table 2). These percentages are similar to those for studies FDA required sponsors to complete.

Table 2: Status of Postmarketing Studies Requested under the Accelerated Approval Process, June 19, 1992–November 20, 2008

Status of open studies	Number of studies (% of Total)
Pending	57 (18%)
Ongoing	21 (7%)
Delayed	6 (2%)
Terminated	0 (0%)
Submitted	30 (9%)
Total open	**114 (36%)**
Status of closed studies	
Fulfilled	166 (52%)
Released	37 (12%)
Total closed	**203 (64%)**
Total	**317 (100%)**

Source: GAO analysis of FDA data.

Note: Status as of January 6, 2009.

Based on information FDA provided, we found that the length of time studies have been open varies by status. Specifically, those studies classified as pending had been open, on average, for about 5.5 years, with more than 40 percent pending for over 8 years. In addition, studies classified as ongoing and delayed had been open, on average, for 5.3 and 4 years respectively, and those classified as submitted have been open on average about 5.6 years.[33] We could not calculate the amount of time it

[32]Status information on requested postmarketing studies under the accelerated approval process was provided by FDA as of January 6, 2009.

[33]We determined the amount of time studies had been open by measuring the amount of time which elapsed from the date the study was requested to January 6, 2009.

took sponsors to close a requested study, because, according to FDA, the dates studies were fulfilled or released were not readily available.

FDA Approved about One-Third of NME Drug Applications Based on Surrogate Endpoints through Its Traditional Process and about Half of the Postmarketing Studies Requested Have Been Closed

From January 1, 1998, through June 30, 2008, FDA approved about one-third of NME drug applications based on surrogate endpoints under its traditional process. Many of these applications were for drugs to treat cancer, heart disease, and diabetes. FDA requested 175 postmarketing studies associated with these NMEs, and about one-half have been classified by FDA as closed.

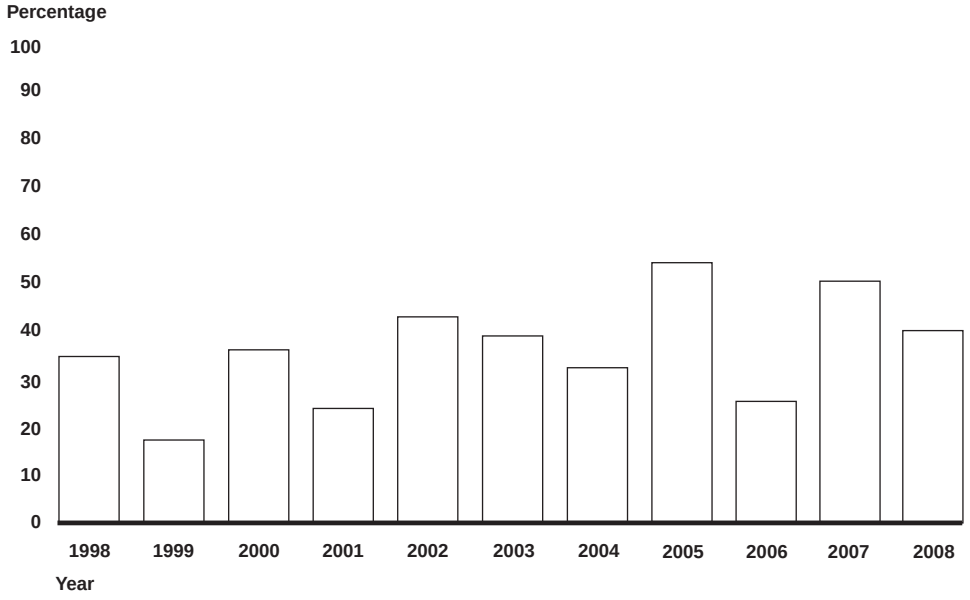
About One-Third of the Applications for NME Drugs Approved under the Traditional Process Were Based on Surrogate Endpoints, Many for Drugs to Treat Cancer, Cardiovascular Disease, and Diabetes

From January 1, 1998, through June 30, 2008, FDA approved 204 applications for NMEs to treat diseases through the traditional approval process.[34] Of these 204 applications, FDA approved 69, or about 34 percent, on the basis of surrogate endpoints.[35] The percentage of NME approvals based on surrogate endpoints per year varied, ranging from 17 percent in 1999 to 54 percent in 2005. Additionally, in most years from January 1998 through June 2008, NME applications that were approved based on surrogate endpoints comprised less than half of all NME approvals in any given year (see fig. 6).

[34]In addition to these 204 NMEs, FDA approved an additional 15 NMEs for drugs used to aid in diagnosing diseases or in aiding the absorption of other drugs. Because these 15 were not used to treat a disease, we excluded them from our analyses.

[35]These 69 applications include one for a drug that was approved for many indications (diseases). This drug was approved for some of these indications primarily based on a surrogate endpoint and some were approved based on a clinical endpoint. Therefore, we included this drug in our scope.

Figure 6: Percentage of Applications for NME Drugs Approved Using Surrogate Endpoints under FDA's Traditional Approval Process, January 1, 1998–June 30, 2008



Source: GAO analysis of FDA data.

Note: 2008 data include NME drug approvals only through June 30, 2008.

The most frequently used surrogate endpoints in the traditional process were those to establish the effectiveness of drugs to treat cancer, cardiovascular disease, and diabetes. Specifically, 13 of the 69 applications—or 19 percent of applications approved—were for drugs to treat cancer, using various tumor assessments as surrogate endpoints, including response rates, similar to those used in the accelerated process. In addition, 11 of the 69 applications, or 16 percent, were approved for drugs to treat cardiovascular disease, based on their ability to decrease blood pressure or control cholesterol levels. Furthermore, 10 of the 69, or 14 percent were for diabetes drugs, based on their ability to lower blood sugar levels (see table 3). Drugs to treat a variety of other diseases—including renal disease and hepatitis B—accounted for the remaining 35 applications, and their approval was based on a variety of surrogate endpoints (app. II contains a list of individual drugs, application numbers, and specific surrogate endpoints used for approval of NME drugs through the traditional approval process).

Table 3: Summary of Surrogate Endpoints for NME Drug Application Approvals, from January 1, 1998–June 30, 2008

Disease	Surrogate endpoint(s) used for approval	Number of applications
Cancer	• Tumor assessment • Time to progression • Response rate • Progression-free survival • Other (e.g., serum testosterone levels)	13
Cardiovascular conditions	• Blood pressure • Lipid levels (cholesterol and triglycerides)	11
Diabetes mellitus	• Blood sugar • Fasting plasma glucose levels • HbA1c levels	10
Other diseases	• Various	35
	Total	**69**

Source: GAO analysis of FDA data.

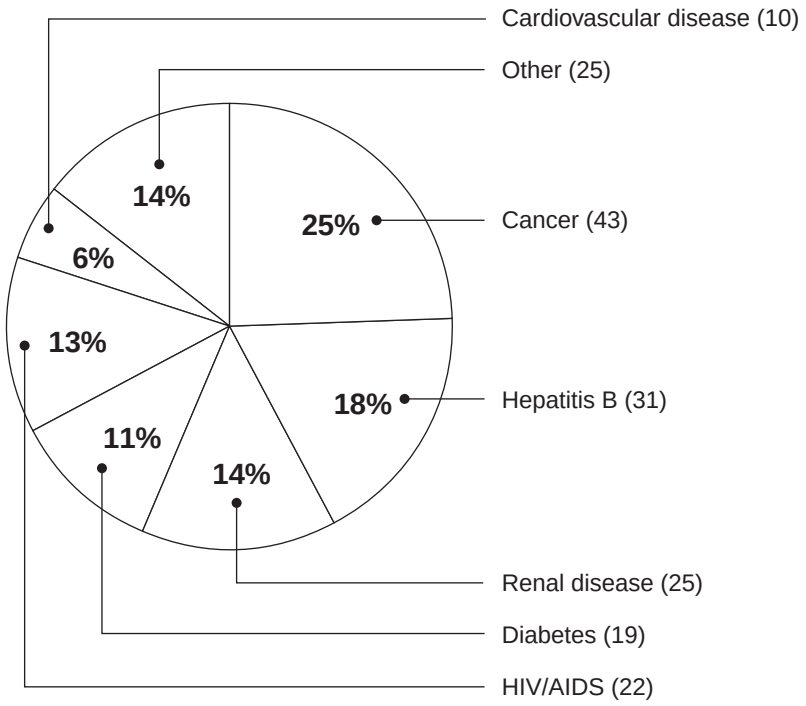
Our analysis of NME drug applications represents only a small subset of all applications which FDA may have approved based on surrogate endpoints under the traditional approval process during this time period. From January 1, 1998, through June 30, 2008, FDA approved about 2,000 other applications; however, it does not track whether they approved these applications based on surrogate endpoints. Thus the extent to which FDA used these and other surrogate endpoints as a basis for approval is unclear.[36]

[36]FDA and others have suggested that the identification of validated surrogate endpoints already used in drug approvals, as well as criteria for accepting new potential surrogate endpoints, may encourage more efficient drug development. See GAO, *New Drug Development: Science, Business, Regulatory and Intellectual Property Issues Cited as Hampering Drug Development Efforts*, GAO-07-49 (Washington, D.C.: Nov. 17, 2006). FDA planned to develop a comprehensive inventory of all surrogate endpoints used to approve new drugs, including those under the traditional process. FDA officials told us that they were able to compile a partial list of such endpoints, but due to other competing priorities, this inventory was never completed.

FDA Requested 175 Postmarketing Studies under Its Traditional Process, and About One-Half Have Been Closed

From January 1, 1998, through June 30, 2008, FDA requested 175 postmarketing studies for NMEs approved based on surrogate endpoints under the traditional process. During this time frame, FDA requested studies for drugs to treat a variety of diseases. Of the 175 studies, FDA requested 43, or 25 percent, for drugs to treat cancer. In addition, FDA requested 31 studies, or 18 percent, for drugs to treat hepatitis B. The remaining studies were for drugs to treat a variety of other diseases, including renal disease, diabetes, HIV/AIDS, and cardiovascular disease (see fig. 7).

Figure 7: Percentage of Postmarketing Studies Requested under the Traditional Process, by Disease, January 1, 1998–June 30, 2008



Source: GAO analysis of FDA data.

Based on the status FDA assigned each study at the time of our review, FDA had classified 94 of the 175 requested studies, or 54 percent, as closed, meaning that drug sponsors had satisfied FDA's request for these studies or FDA determined the studies were no longer needed or feasible. Additionally, we found that FDA had classified 81, or 46 percent, as open, and sponsors had made varying levels of progress in completing them (see table 4).

Table 4: Status of Postmarketing Studies Requested under the Traditional Approval Process, January 1, 1998–June 30, 2008

Status of open studies	Number of studies (% of Total)
Pending	33 (19%)
Ongoing	21 (12%)
Delayed	7 (4%)
Terminated	4 (2%)
Submitted	16 (9%)
Total open	**81 (46%)**
Status of closed studies	
Fulfilled	87 (50%)
Released	7 (4%)
Total closed	**94 (54%)**
Total	**175 (100%)**

Source: GAO analysis of FDA data.

Note: Status as of February 13, 2009.

Based on information FDA provided, we found that the length of time studies have been open varies by status. Specifically, those studies classified as pending had been open, on average, for 3.8 years, ranging from less than 1 year to 10.9 years. In addition, studies classified as ongoing and delayed had been open, on average, for 2.9 and 5.8 years respectively, and those classified as submitted have been open on average 4.2 years.[37] We could not calculate the amount of time it took sponsors to close a requested study, because, according to FDA, the dates studies were fulfilled or released were not readily available.

[37]We determined the amount of time studies had been open by measuring the amount of time which elapsed from the date the study was requested to February 13, 2009.

FDA's Oversight of Postmarketing Studies Is Hindered by Weaknesses in Its Monitoring and Enforcement

FDA has not been routinely monitoring the status of postmarketing studies, primarily because oversight of these studies is not considered a priority. Regarding its enforcement of postmarketing study requirements, we found FDA has not fully utilized its available enforcement tools, even when sponsors have failed to complete required studies.

FDA Has Not Been Routinely Monitoring the Status of Postmarketing Studies, although Initiatives to Improve Its Monitoring Are Underway

FDA has not been routinely reviewing ASRs to confirm the accuracy of information and verify the status of studies within its goal of 90 days. Our review of information provided by FDA for 35 specific required postmarketing studies showed that just over half of the ASRs provided for 19 of these studies had never been reviewed by FDA medical reviewers, and that for those that had been reviewed, about half were not done in a timely manner (see app. III for a copy of the information request we submitted to FDA for these postmarketing studies). FDA medical reviewers indicated that they were not able to complete scheduled reviews of ASRs, and according to FDA officials, this task was a lower priority compared to their other responsibilities, such as review of applications for new drugs.

This finding is consistent with the results reported by the HHS-OIG in 2006[38] as well as FDA's contractor, Booz Allen Hamilton, in 2008.[39] Both found that FDA was not completing reviews of ASRs in a timely manner and had not made such reviews a priority. For example, the HHS-OIG 2006 study, which examined FDA's review of ASRs submitted during fiscal year 2004, found that FDA did not meet its goal of reviewing ASRs in 90 days 55 percent of the time. For 26 percent of these ASRs, it took FDA more than 180 days to complete its review. Similarly, the contractor's study, which examined FDA's review of ASRs for requested studies, found that FDA reviewers were missing the agency's goal of reviewing ASRs in 90 days

[38]For more information, see HHS' Office of Inspector General's report entitled *FDA's Monitoring of Postmarketing Study Commitments* (June 2006).

[39]FDA retained Booz Allen Hamilton in 2006 to conduct an independent analysis of the agency's postmarket processes and procedures. In *Postmarketing Commitments Study Final Report*, issued in January 2008, the contractor highlighted further problems, and made recommendations designed to improve FDA's monitoring and oversight of postmarketing studies.

47 percent of the time. Both HHS-OIG and the contractor reported that the monitoring of postmarketing studies is not a top priority of the agency. Specifically, the HHS-OIG reported that FDA officials indicated that other tasks, including reviewing drug applications and documenting FDA/industry meetings, are higher priorities than reviewing postmarketing studies and ASRs. In addition, the contractor similarly reported that a reason for missing review deadlines was heavy reviewer workload and that postmarketing study review-related tasks, including review of ASRs, were often given a lower priority as compared to application reviews.

Without routine monitoring, FDA's database does not contain complete and reliable information, including key dates and study information needed to track the progression of postmarketing studies. When we requested information on time frames associated with the progression of postmarketing studies, FDA could not provide it to us from its database. This is because FDA had not entered into the database the key dates such as when studies started, are scheduled for completion, and their current status. To provide us with the information we requested, FDA had to comb through multiple data systems and paper files to recreate milestones and status outcome by study. This problem is not new. The HHS-OIG reported in 2006 that FDA was not entering into the database the information from ASRs, noting, for example, that for primarily requested studies, the study start dates were present for only 6 percent and original projected completed dates were present for only 21 percent. As a result, the HHS-OIG recommended that FDA improve its database for monitoring postmarketing studies so that it provides timely, accurate, and useful information and ensure that studies are being monitored.

Given that FDA's medical reviewers are not routinely reviewing ASRs and do not have reliable information readily available to track the status of postmarketing studies, the agency cannot effectively monitor these studies. FDA does not know the current status of many postmarketing studies or whether they are progressing towards completion. In addition, FDA does not know whether drug sponsors are submitting complete and accurate ASRs in a timely manner. As a result, FDA lacks current, reliable, and easily accessible information on the status of open postmarketing studies, and meeting federal reporting requirements is difficult.[40] The

[40]FDA is required to report annually in the *Federal Register* and to congressional committees the status of postmarketing studies that are the subject of annual status reports submitted to FDA. 21 U.S.C. §§ 356b(c), 356b note.

information available regarding postmarketing studies can only be as accurate and complete as the data contained in FDA's postmarketing database.

FDA has three initiatives in place to address the agency's oversight weaknesses. First, to ensure FDA has current information on the status of open postmarketing studies and facilitate the timely review of ASRs, FDA retained the contractor in 2008 to review ASRs for all postmarketing studies classified as open. As part of this effort, the contractor will support the work performed in FDA's medical review divisions and conduct an initial review of all newly submitted ASRs. This initial review is intended to help ensure that ASRs are reviewed within FDA's 90-day review goal. Based on its review, the contractor will determine whether the status of the postmarketing studies that sponsors listed in the ASR is correct, and meet biweekly with FDA staff to discuss ongoing issues. FDA staff will use this information to determine the appropriate status of open studies and update its tracking database.[41] This year FDA renewed its contract with Booz Allen Hamilton, which is now scheduled to expire in 2014, to continue review of outstanding and new ASRs associated with postmarketing studies.

The second initiative is the creation of a new tracking coordinator position within each medical review division with responsibility for a variety of tasks related to the tracking of postmarketing studies. First, the tracking coordinators will ensure that reviewers are kept informed of key postmarketing schedule dates. They will also verify the accuracy of postmarketing study information and monitor whether expected activities are conducted within specified time lines. Further, the coordinator will serve as a key point of contact to interface with the contractor and ensure that status information provided by the contractor is entered into the postmarketing database. Currently, tracking coordinator responsibilities are shared between other existing positions within the divisions. FDA officials indicated that they were not sure whether the tracking coordinator position would be filled by one person in each medical review division or if the duties would be divided among many individuals in each division.

[41]According to FDA officials, their contractor has already identified numerous instances where status information was incorrect, such as when studies listed as pending were, in fact, ongoing. Based on this information FDA will be updating its database with the correct information, and this will be reflected in its next annual report in the *Federal Register*.

To the extent that the ASR reviews and tracking coordinator initiatives are successful, FDA's third initiative—the Document Archiving, Reporting and Regulatory Tracking System (DARRTS)—could facilitate the monitoring of postmarketing studies for NDAs.[42] DARRTS is a Web-based system, which according to FDA officials should allow FDA staff greater access to information and provide enhancements over the current database, such as creating management reports on specific drugs and their respective studies.

FDA Has Not Fully Utilized Its Enforcement Tools Related to Required Postmarketing Studies

FDA has not fully utilized its two enforcement tools—issuing administrative action letters and withdrawing a drug from the market in certain cases—to encourage and compel drug sponsors to complete required confirmatory postmarketing studies. FDA has the discretion to issue administrative action letters to drug sponsors if 1) sponsors are late or fail to submit ASRs, or 2) FDA determines that sponsors are not sufficiently progressing in completing their studies.

The extent to which FDA has issued administrative action letters related to its oversight of postmarketing studies required under the accelerated approval process is unclear. According to FDA officials, they do not have a centralized database which tracks the letters they have issued to sponsors when sponsors were late or failed to submit ASRs, or when FDA determined that sponsors were not sufficiently progressing in completing their studies. Our review of FDA's oversight of a sample of postmarketing studies required under the accelerated approval process suggests its use may be limited when sponsors do not submit their ASRs within required time frames. Specifically, we found that sponsors were late in submitting ASRs for 12 postmarketing studies in our sample. However, FDA issued an administrative action letter to the sponsor of only 1 of these 12 studies.

In addition to sending administrative action letters for drugs approved under the accelerated approval process, FDA also may begin expedited proceedings to withdraw a drug's approval in a number of situations including if it determines that: 1) sponsors are not completing required confirmatory postmarketing studies with due diligence, or 2) a study failed to confirm the drug's clinical benefit. According to FDA officials, the

[42]DARRTS became operational for NDAs in July 2009. FDA will continue to use its current system to oversee postmarketing studies related to BLAs. Data related to BLAs are scheduled to be integrated into DARRTS in 2010.

agency has never withdrawn from the market a drug approved through the accelerated process due to either of these issues. Our review of the 90 applications approved based on a surrogate endpoint under the accelerated approval process revealed several circumstances that appeared to meet the regulatory conditions for withdrawal, but FDA was hesitant to use its enforcement authority. Specifically, we found that for 36 of the 90 applications, drug sponsors had not fulfilled their confirmatory study requirements by establishing the clinical effectiveness of those drugs. This includes several applications for drugs that FDA had approved more than 10 years ago and for which sponsors had not yet completed all of their required studies, and others where the studies failed to confirm the drug's clinical effectiveness. An example of sponsors not completing confirmatory studies includes the case of ProAmatine:

- FDA approved ProAmatine in 1996 to treat individuals with low blood pressure based on the surrogate endpoint of raising 1-minute standing systolic blood pressure. As a condition of approval, it required the sponsor, Shire Pharmaceuticals, to conduct a confirmatory study to validate long-term clinical benefits. However, the sponsor was not able to design and conduct a sufficiently adequate clinical study, and the clinical benefit of the drug has never been established. Despite this, the sponsor benefited from market exclusivity between 1996 and 2003, and sales of this drug generated millions of dollars for the company (see app. IV for total U.S. sales since approval for ProAmatine and six other drugs for which applications had not converted to full approval as of December 19, 2008). Furthermore, once ProAmatine's market exclusivity ended in 2003, FDA approved five generic versions of the drug, although the clinical benefit of the drug was never confirmed. Recognizing that the study requirement related to ProAmatine was still outstanding; in August 2007 FDA posted a letter on its Web site inquiring about certain legal and regulatory issues related to the generic manufacturers' potential completion of the confirmatory study. In August 2008, according to officials, FDA posted another letter in which it threatened to withdraw approval of ProAmatine and the generic drugs based on its accelerated approval authority if no company completed the required studies.[43] At the same time it indicated that 3 years of market exclusivity would be available if a company completes the study and it confirms clinical benefit. As of June 2009, nearly 13 years after it approved ProAmatine, FDA had not initiated the

[43]According to FDA officials, the agency did not mail these letters directly to the five generic manufacturers, but contacted certain key industry officials regarding FDA's posting of these letters.

withdrawal of ProAmatine or the generic versions, but FDA officials indicated that it planned to issue a final administrative action letter to the sponsor and generic manufacturers in a final effort to obtain completion of the required study.

An example of sponsors completing confirmatory studies which failed to confirm the drug's clinical effectiveness includes the case of Iressa:

- FDA approved Iressa in May 2003 to treat patients with non-small cell lung cancer based on the surrogate endpoint that showed that it causes significant shrinkage in tumors in about 10 percent of patients. As a condition of approval, FDA required the sponsor to conduct a postmarketing study to verify the expected clinical benefit. In December 2004, FDA announced that the results of the clinical trial in 1,700 patients indicated that the drug did not prolong survival. Despite this, FDA did not utilize its authority to withdraw the drug from the market. However, it did take the step of restricting Iressa's use to a subset of patients who had already taken the medicine and whose doctor believed it was helping them. FDA directed new patients wanting to take Iressa to two other available therapies shown in studies to improve survival in patients whose cancer has progressed while on previous therapies.

According to FDA officials, they have not developed guidance to specify the conditions under which they would exercise their authority to withdraw approval of a drug that the agency approved based on surrogate endpoints under the accelerated approval process. Under the regulations, FDA can initiate expedited withdrawal procedures for drugs approved based on surrogate endpoints when sponsors fail to perform required confirmatory postmarketing studies with due diligence, or a study failed to confirm the drug's clinical effectiveness. Although the regulations outline conditions under which FDA could utilize expedited withdrawal authority for drugs approved under the accelerated approval process based on surrogate endpoints, withdrawal is not required and the agency has latitude in determining when to exercise this authority. The officials recognized that they have not specified criteria for defining how they would implement the due diligence requirement of the regulations, such as determining how long it should take a sponsor to complete a study or when a sponsor is taking too long, which could result in a drug's withdrawal from the market. Without such guidance, officials indicated that it is not clear as to when or how to enforce the due diligence criteria for withdrawal, but acknowledged that ProAmatine may have been a case where they could have fully utilized their withdrawal authority. Officials further stated that it would be difficult to develop specific criteria for due

diligence for withdrawal that could be generally applied to the wide range of diseases treated by drugs approved under the accelerated approval process. Additionally, they questioned the need for such specific criteria, because other than the case of ProAmatine, they have rarely faced circumstances where drug sponsors were reluctant to work toward completing their postmarketing study. Regarding cases when a confirmatory study failed to demonstrate a drug's clinical benefit, agency officials indicated they would be hesitant to withdraw a drug in such cases. For example, they said that despite the confirmatory study results, Iressa may still be effective for a number of patients.

Conclusions

The use of surrogate endpoints has been accepted by FDA as a means of demonstrating the efficacy of drugs approved through both its traditional and accelerated approval processes. While the use of surrogate endpoints can expedite the approval of drugs, reliance on these endpoints also introduces uncertainty regarding the risks and benefits of a drug because the clinical effectiveness is not directly measured. Thus their use can lead to the adoption of useless or even harmful therapies if the effect on a surrogate endpoint does not accurately predict whether treatments provide benefits to patients, or if the drug has a smaller than expected benefit and a larger than expected adverse effect.

With the creation of the accelerated approval process in 1992, FDA expanded the use of surrogate endpoints, thus expediting the approval of certain drugs for serious or life-threatening diseases. While the availability of these drugs provided new treatment options to patients, it also introduced new elements of uncertainty, as FDA allowed the use of surrogate endpoints which had not yet been shown to be valid predictors of a drug's clinical effectiveness. Thus, patients could potentially find themselves taking drugs approved under the accelerated process that may not be clinically effective in treating their illness. Recognizing the need to mitigate this uncertainty and risk, FDA required that drug sponsors conduct postmarketing studies with due diligence to confirm that such drugs actually have clinical benefits. It also implemented a process for monitoring the progression and completion of these studies, including establishing a database to track the progression of the studies, and instituting expedited withdrawal procedures for drugs when studies are not completed or if they failed to confirm clinical benefits.

Despite these tools, weaknesses in FDA's monitoring and enforcement process hamper its ability to effectively oversee postmarketing studies. FDA has not routinely and consistently reviewed the ASRs submitted by

drug sponsors, and information the agency needs to ensure that sponsors are completing required confirmatory studies in a timely manner was not consistently entered into its tracking database. Therefore, the agency has lacked an effective management information system capable of generating data needed to effectively monitor the progress of such studies. FDA has recently implemented several initiatives to enhance its oversight of postmarketing studies, which may provide the agency with an opportunity to develop reliable data needed to adequately monitor the progress of studies and improve oversight. Additionally, FDA's plans to designate personnel to serve as focal points for monitoring postmarketing studies may provide a greater emphasis on oversight of such studies. It is too early to tell if these initiatives will be successful. While FDA's new system, DARRTS, may have features superior to the tracking database it is replacing, the root cause of many problems associated with the previous system was not the system itself, but the failure to enter information into it. The ultimate success of FDA's new initiatives is largely dependent on the timely review and prompt entry of ASRs into DARRTS.

While FDA has implemented measures to enhance its monitoring of postmarketing studies, the agency has taken a passive approach to enforcing confirmatory study requirements. It has never exercised its authority to withdraw a drug it approved based on surrogate endpoints under the accelerated approval process, even when such studies have been outstanding for nearly 13 years. Further, FDA has not attempted to clarify the circumstances under which it would exercise this authority and has never developed specific time frames for sponsors to complete their confirmatory studies. The combination of its ineffective monitoring and lack of criteria outlining when a drug should be withdrawn from the market make it difficult for FDA to utilize its enforcement authority. Consequently, drugs which have not proven to be clinically effective may remain on the market while their associated confirmatory studies remain incomplete.

Recommendations

To clarify FDA's enforcement authority under the accelerated approval process, we recommend that the Commissioner of FDA take the following action:

- Clarify the conditions under which the agency would utilize its authority to expedite the withdrawal of drugs approved based on surrogate endpoints under the accelerated approval process if sponsors either fail to complete required confirmatory studies with due diligence, or if studies are completed, but fail to demonstrate the clinical effectiveness of the drugs.

Agency Comments and Our Evaluation

We provided a draft of this report to HHS for review. HHS provided written comments from FDA, which are reprinted in appendix V. In its comments, FDA disagreed with our recommendation to clarify the conditions under which it would utilize its authority to expedite the withdrawal of drugs approved based on surrogate endpoints under the accelerated approval process. FDA also said that it thought we minimized the success of the accelerated approval program. The agency stressed that this program has provided millions of patients access to new treatments sooner than would have been possible under the traditional approval process. In addition, FDA described its efforts to improve monitoring of the completion of required and requested postmarketing studies. FDA also provided technical comments, which we incorporated as appropriate.

Regarding our recommendation, FDA indicated that it would be difficult, if not impossible, to provide further clarification as to when it might utilize its authority to expedite withdrawal of a drug approved on the basis of surrogate endpoints. FDA acknowledged that there have been cases where confirmation of the clinical benefit of drugs approved under the accelerated approval program did not occur in a timely manner. However, FDA stressed that, unless there are clear safety concerns emanating from the confirmatory trial, it must carefully assess each case and consider the underlying reasons and consequences of all regulatory options, including their potential impact on patients. In expressing its disagreement and the need for case-by-case assessments, FDA cited the examples of two drugs mentioned in our report—ProAmatine and Iressa. In the case of ProAmatine, for which adequate clinical trials have never been completed to establish the drug's benefit, FDA stated that it would not be appropriate to initiate expedited withdrawal, as ProAmatine is the only approved therapy for the condition that it treats. FDA stated that rather than providing an example of the agency failing to exercise its authority to withdraw approval, ProAmatine provides a good example of the complex issues it must consider when a clinical benefit has not been confirmed and the drug approved remains the only FDA-approved treatment for a serious or life-threatening condition. Regarding Iressa, FDA noted that, despite the fact that the clinical trials failed to confirm the drug's clinical benefit, they nonetheless suggested there were some positive outcomes for certain patients. Therefore, rather than withdraw approval of Iressa, FDA indicated that it took an appropriate and balanced approach by restricting access to those patients who were already receiving treatment and whose physicians felt they were benefiting from Iressa and to other patients based on physician assessments.

We recognize that FDA faces challenges in determining whether it should initiate the expedited withdrawal of a drug approved under the accelerated approval process. Acknowledging that the clinical benefit of these drugs is uncertain at the time of their approval, FDA's 1992 regulations provided that expedited withdrawal of drugs may be appropriate when confirmatory studies fail to show clinical benefits. Indeed, FDA's ability to require sponsors to complete clinical trials with due diligence and its authority to undertake the expedited withdrawal of a drug if a clinical benefit is not confirmed are specifically cited by FDA in its comments as two important safeguards intended to minimize the risks inherent in the accelerated approval process. Although nearly 17 years have elapsed since FDA issued the accelerated approval regulations, the agency has not attempted to define the circumstances under which the authority that this important safeguard provides would be used.

While FDA commented that it would consider exercising its withdrawal authority if a clear safety concern emerged from a confirmatory trial, which would certainly be appropriate, the regulations governing the use of surrogate endpoints and the purpose of the required studies are focused on establishing the clinical benefit of a drug, not its safety. We agree that it may be challenging for FDA to develop guidance to clarify the conditions under which it would utilize its expedited withdrawal authority. However, we do not agree that it is impossible—or even too difficult—to do so, nor do we believe that such guidance would have to be so prescriptive as to prevent FDA from considering the unique circumstances of individual cases. As the scientific experts charged with overseeing the use of drugs it approves, FDA should be in a position to implement this recommendation. In our view, this would serve two purposes. First, this would clarify within FDA when this option should be considered in order to mitigate risks to patients taking drugs which FDA has approved. Second, it would serve to clarify, for drug sponsors, FDA's expectations regarding performance requirements related to completing required confirmatory studies, and the consequences of not meeting requirements. This would put drug sponsors on notice that, although FDA has not utilized this authority to date, it remains a viable option, and would enhance the agency's ability to effectively carry out its oversight responsibilities. Without specific parameters governing the use of this authority, such as definitive time frames or other requirements for when sponsors need to complete confirmatory studies, there appears to be little likelihood that FDA would ever utilize its authority, thus potentially diminishing the value of what FDA considers an important safeguard.

Regarding the examples of ProAmatine and Iressa, we recognize that FDA faced numerous scientific and ethical issues in overseeing the use of these drugs, and that it ultimately needed to balance such factors when determining the best approach to take in overseeing the completion of required confirmatory studies. However, we chose to discuss these drugs because the very circumstances surrounding them illustrated specific oversight issues which FDA considered when it developed the 1992 accelerated approval regulations. The circumstances involving these drugs also highlighted the challenges that FDA faces in determining how to conduct its oversight responsibilities. As delineated in the regulations, the purpose of these confirmatory studies is to verify and describe the clinical benefits of these drugs. When sponsors fulfill these requirements, they establish the clinical evidence similar to what would ordinarily have been required were the drugs reviewed under the traditional approval process. In neither of these two instances has this level of evidence been established—no adequate study has ever been completed to confirm the clinical benefits of ProAmatine and, while the studies for Iressa were conducted, they failed to confirm any clinical benefit.

Specifically, in the case of ProAmatine, as we noted in our report, FDA officials acknowledged that this matter may have gone on too long without being resolved. Although FDA's comments indicate that it believes the sponsor conducted trials with due diligence, 13 years have elapsed, and although the drug is also available generically, sufficient confirmatory trials have not been completed. As FDA indicates in its comments, obtaining the completion of the trials has become a complex matter and it is still seeking ways to encourage one or more of the generic manufacturers to conduct the confirmatory clinical trials. Thus, we believe that this example raises questions about whether the sponsor had displayed due diligence in meeting the confirmatory study requirements as well as what circumstances would lead the agency to exercise its withdrawal authority. We provided the example of Iressa to illustrate the challenges that FDA faces in overseeing the accelerated approval process. In developing the 1992 regulations, FDA specifically anticipated a situation similar to that posed by Iressa—the completion of a confirmatory study that failed to demonstrate a drug's clinical benefit. Although 17 years have passed, FDA has not established guidance clarifying how it would exercise its expedited withdrawal authority in such circumstances. While FDA's actions in these two cases may have been appropriate, they nonetheless serve to illustrate the need to clarify use of the expedited withdrawal authority, consistent with our recommendation.

Regarding FDA's statement that the accelerated approval process has been very successful, and has resulted in the early approval of many significant therapeutic advances for patients, we believe that this conclusion is a matter of scientific judgment, and beyond the scope of our review. However, our report clearly identified both the purpose of the accelerated approval process, and the specific drugs that FDA has approved using this process. Thus, we believe we provide an accurate factual description of the drugs approved on the basis of surrogate endpoints through this process since it was instituted in 1992. Further, we do not believe that our emphasis on examples of FDA's decisions regarding specific drugs and the results of their associated confirmatory studies, in any way minimizes the benefits provided by the accelerated process. Instead they are meant to illustrate challenges associated with FDA's oversight of such an important program.

Finally, regarding FDA's ongoing efforts to improve its oversight of postmarketing studies in both the accelerated and traditional approval processes, FDA acknowledged that its oversight of postmarketing studies in general has been inadequate, and agreed that improvements are needed. The agency indicated that because of inadequate staffing and information technology resources and competing priorities, its past tracking of postmarketing studies has not been timely. FDA stated that it has begun to implement a number of improvements to ensure appropriate oversight, more efficient tracking, and expeditious review of postmarketing submissions from sponsors, but stated that these efforts were not fully reflected in our report. We believe our report's discussion of FDA's efforts to improve the monitoring of postmarketing studies sufficiently addresses FDA's ongoing initiatives. Specifically, we discuss its contract with Booz Allen Hamilton, the establishment of new tracking coordinator positions which are outlined in its revised Manual of Policies and Procedures, and planned improvements in data reporting capabilities through the DARRTS system. In particular, FDA highlighted the results of efforts from its contractor, Booz Allen Hamilton, which FDA said resulted in extensive updating of the data in the agency's tracking database. However, the results of these updates to the database by FDA's contractor became available subsequent to our work, and thus could not be reflected in the data we presented in this report. The fact that extensive updates needed to be made, however, confirms our assessment that FDA's monitoring and oversight has been ineffective. We are encouraged that FDA is taking steps to facilitate timely oversight of postmarketing studies through improved tracking provided by its contractor and a new database.

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 to the Commissioner of FDA and appropriate congressional committees. The report also will be available at no charge on GAO's Web site 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 major contributions to this report are listed in appendix VI.

Sincerely yours,

Marcia Crosse
Director, Health Care

Appendix I: Applications for Drugs Approved under FDA's Accelerated Approval Process Using Surrogate Endpoints

Since the Food and Drug Administration (FDA) began approving drugs under the accelerated approval process in 1992, it has approved 90 applications based on surrogate endpoints. In several cases, FDA approved multiple applications for the same drug; as a result, as of November 20, 2008, FDA had approved 64 drugs associated with these applications under the accelerated approval process. Table 5 provides a description of each of these 64 drugs, their new drug application (NDA) or biologic license application (BLA) numbers, and the surrogate endpoints used for approval.

Table 5: NDAs and BLAs Approved Based on Surrogate Endpoints under the Accelerated Approval Process, from June 19, 1992–November 20, 2008

Drug name	NDA/BLA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Hivid	20199	June 19, 1992	Monotherapy and combination therapy for treatment of Human Immunodeficiency Virus infection in specific patients	CD4 count (infection fighting white blood cells) and p24 existence (antigen which indicates HIV infection)
Betaseron	103471[a]	July 23, 1993	Treatment of relapsing-remitting multiple sclerosis	MRI evaluations of brain lesions[b]
Biaxin	50697	Dec. 23, 1993	Treatment of disseminated mycobacterial infections due to specific bacteria	Clearance of bacteremia[b]
	50698	Dec. 23, 1993	Treatment of disseminated mycobacterial infections due to specific bacteria	Clearance of bacteremia[b]
Zerit	20412	June 24, 1994	Treatment of advanced Human Immunodeficiency Virus infection in specific adult patients	CD4 count (infection fighting white blood cells) and p24 existence (antigen which indicates HIV infection)
Casodex	20498	Oct. 4, 1995	Combination therapy for the treatment of advanced prostate cancer	Time to treatment failure[b]
Epivir	20564	Nov. 17, 1995	Combination therapy for treatment of Human Immunodeficiency Virus infection in certain circumstances	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
	20596	Nov. 17, 1995	Combination therapy for treatment of Human Immunodeficiency Virus infection in certain circumstances	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
Doxil	50718	Nov. 17, 1995	Treatment of Kaposi's sarcoma in specific patients with Acquired Immunodeficiency Syndrome	Response rate[c]
	50718-SE1-006	June 28, 1999	Treatment of metastatic carcinoma of the ovary in specific patients	Response rate[c]
Invirase	20628	Dec. 6, 1995	Combination therapy for treatment of advanced Human Immunodeficiency Virus infection in specific patients	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)

Drug name	NDA/BLA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Norvir	20659	Mar. 1, 1996	Treatment of Human Immunodeficiency Virus infection	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
	20680	Mar. 1, 1996	Treatment of Human Immunodeficiency Virus infection	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
Crixivan	20685	Mar. 13, 1996	Treatment of Human Immunodeficiency Virus infection when antiretroviral therapy is warranted	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
Ethyol	20221-SE1-002	Mar. 15, 1996	Treatment for the toxicities associated with intensive regimens of specific chemotherapy	Creatinine clearance and response rate to assess tumor protection
Taxotere	20449	May 14, 1996	Treatment of locally advanced or metastatic breast cancer in specific patients	Response rate[c]
Camptosar	20571	June 14, 1996	Treatment of metastatis carcinoma of the colon or rectum in certain circumstances	Response rate[c]
Viramune	20636	June 21, 1996	Combination antiretroviral treatment for Human Immunodeficiency Virus infection in specific patients	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
	20636-SE1-009	Sept. 11, 1998	Combination antiretroviral treatment for Human Immunodeficiency Virus-1 infection in pediatric patients	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
	20933	Sept. 11, 1998	Combination antiretroviral treatment for Human Immunodeficiency Virus-1 infection in pediatric patients	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
ProAmatine	19815	Sept. 6, 1996	Treatment of idiopathic orthostatic hypotension	Increase in 1-minute standing systolic blood pressure
Viracept	20778	Mar. 14, 1997	Treatment of Human Immunodeficiency Virus infection in children when antiretroviral therapy is indicated	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
	20779	Mar. 14, 1997	Treatment of Human Immunodeficiency Virus infection when antiretroviral therapy is indicated	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
Rescriptor	20705	April 4, 1997	Treatment of Human Immunodeficiency Virus-1 infection	CD4 count (infection fighting white blood cells) and viral load (HIV-RNA)
Xeloda	20896	April 30, 1998	Treatment of a specific type of metastasis breast cancer in certain patients	Response rate[c]
Sulfamylon	19832	June 5, 1998	Treatment of bacterial infections in certain circumstances	Necessity to change topical antimicrobial treatment during the first 5 days of application due to infection or colonization

Drug name	NDA/BLA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Priftin	21024	June 22, 1998	Treatment of pulmonary tuberculosis	Negative sputum culture at 6 month post-treatment (6 month relapse rate)
Sustiva	20972	Sept. 17, 1998	Treatment of Human Immunodeficiency Virus infection	Viral load (HIV-RNA)
Ziagen	20977	Dec. 17, 1998	Combination antiretroviral treatment for Human Immunodeficiency Virus infection	Viral load (HIV-RNA)
	20978	Dec. 17, 1998	Combination antiretroviral treatment for Human Immunodeficiency Virus infection	Viral load (HIV-RNA)
Ontak	103767[a]	Feb. 5, 1999	Treatment of a specific type of persistent or recurrent Cutaneous T-cell Lymphoma	Response rate[c]
DepoCyt	21041	April 1, 1999	Treatment of lymphmatous meningitis	Response rate (complete cytologic response with absence of neurologic progression)[c]
Agenerase	21007	April 15, 1999	Combination antiretroviral treatment for Human Immunodeficiency Virus-1 infection	Viral load (HIV-RNA)
	21039	April 15, 1999	Treatment of Human Immunodeficiency Virus infection	Viral load (HIV-RNA)
Temodar	21029	Aug. 11, 1999	Treatment of refractory anaplastic astrocytoma in specific adult patients	Progression free survival at 6 months and objective response
Synercid	50747	Sept. 21, 1999	Treatment of serious or life-threatening infections associated with vancomycin-resistant enterococcus faecium bacteremia	Clearance of vancomycin-resistant Enterococcus faecium bacteremia
Celebrex	21156	Dec. 23, 1999	To reduce the number of adenomatous colorectal polyps in familial adenomatous polyposis, and as an adjunct to usual care	Mean reduction in colorectal polyp count
Mylotarg	21174	May 17, 2000	Treatment of CD33+ acute myeloid leukemia in specific patients	Complete responses (blasts, bone marrow, CBC, transfusions)[c]
Cipro	19537-SE1-038	Aug. 30, 2000	Treatment of inhalation anthrax (post-exposure)	Serum CIPRO concentrations
	19847-SE1-024	Aug. 30, 2000	Treatment of inhalation anthrax (post-exposure)	Serum CIPRO concentrations
	19857-SE1-027	Aug. 30, 2000	Treatment of inhalation anthrax (post-exposure)	Serum CIPRO concentrations
	19858-SE1-021	Aug. 30, 2000	Treatment of inhalation anthrax (post-exposure)	Serum CIPRO concentrations
	20780-SE1-008	Aug. 30, 2000	Treatment of inhalation anthrax (post-exposure)	Serum concentrations (compared to effective animal concentrations)

Drug name	NDA/BLA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Kaletra	21226	Sept.15, 2000	Combination antiretroviral treatment for Human Immunodeficiency Virus-1 infection in specific patients	Viral load (HIV-RNA)
	21251	Sept. 15, 2000	Combination antiretroviral treatment for Human Immunodeficiency Virus-1 infection in specific patients	Viral load (HIV-RNA)
Trizivir	21205	Nov. 14, 2000	Treatment of Human Immunodeficiency Virus infection	Viral load (HIV-RNA)
Campath	103948[a]	May 7, 2001	Treatment of B-cell chronic lymphocytic leukemia in specific patients	Response rate[c]
Gleevec	21335	May 10, 2001	Treatment of chronic myeloid leukemia in certain circumstances	Hematologic/cytogenic response
	21335-SE1-001	Feb. 1, 2002	Treatment of Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors	Response rate[c]
	21335-SE1-004	Dec. 20, 2002	Treatment of Philadelphia chromosome positive chronic myeloid leukemia in specific patients	Time to accelerated phase or blast crisis
	21588	April 18, 2003	Treatment of newly diagnosed adult patients with Philadelphia chromosome positive chronic myeloid leukemia in specific patients under certain circumstances	Hematologic/cytogenic response (CML); response rate (GIST); time to accelerated phase or blast crisis (1st line CML)[c]
	21335-SE5-003	May 20, 2003	Treatment of pediatric patients with Ph+ chronic phase chronic myeloid leukemia whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy	Cytogenic response
	21588-SE5-001	May 20, 2003	Treatment of pediatric patients with Ph+ chronic phase chronic myeloid leukemia whose disease has recurred after stem cell transplant or who are resistant to interferon alpha therapy	Cytogenic response
	21588-SE1-016	Sept. 27, 2006	Treatment of newly diagnosed Philadelphia positive chronic myeloid leukemia in pediatric patients	Major hematologic and complete cytogenic response
Viread	21356	Oct. 26, 2001	Combination antiretroviral treatment of Human Immunodeficiency Virus-1 infection in adults	Viral load (HIV-RNA)
Zevalin	125019[a]	Feb. 19, 2002	Treatment of relapsed or refractory low-grade, follicular or transformed B-cell non-Hodgkin's lymphoma in specific patients	Response rate[c]
Eloxatin	21492	Aug. 9, 2002	Treatment of metastatic carcinoma of the colon or rectum in specific patients	Response rate[c]

Drug name	NDA/BLA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Armidex	20541-SE1-010	Sept. 5, 2002	Adjuvant treatment of postmenopausal women with specific breast cancer	Disease free survival
Fuzeon	21481	Mar. 13, 2003	Combination antiretroviral treatment for Human Immunodeficiency Virus-1 infection in specific patients	Viral load (HIV-RNA)
Fabrazyme	103979[a]	April 24, 2003	Treatment of Fabry disease	Intracellular substrate accumulation in the vascular endothelium
Iressa	21399	May 5, 2003	Treatment of locally advanced or metastatic non-small cell lung cancer in specific patients under certain circumstances	Response rate[c]
Velcade	21602	May 13, 2003	Treatment of multiple myeloma in specific patients under certain circumstances	Response rate[c]
Erbitux	125084[a]	Feb. 12, 2004	In combination with other drugs for the treatment of EGFR-expressing, metastatic colorectal carcinoma in specific patients	Response rate[c]
Truvada	21752	Aug. 2, 2004	Combination antiretroviral treatment for Human Immunodeficiency Virus-1 infection in adults	Viral load (HIV-RNA)
Alimta	21677	Aug. 19, 2004	Treatment of patients with locally advanced or metastatic non-small cell lung cancer after prior chemotherapy	Response rate[c]
Luveris	21322	Oct. 8, 2004	Concomitantly use for stimulation of follicular development in infertile hypogonadotropic hypogonadal women with profound LH deficiency	Follicular development
Femara	20726-SE1-011	Oct. 29, 2004	Extended adjuvant treatment of early breast cancer in specific postmenopausal women	Disease free survival
	20726-SE1-012	Dec. 28, 2005	Adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer	Disease free survival
Levaquin	20634-SE1-035	Nov. 24, 2004	Treatment of inhalation anthrax (post-exposure)	Drug exposure in surviving Rhesus monkeys compared to human plasma concentrations
	20635-SE1-035	Nov. 24, 2004	Treatment of inhalation anthrax (post-exposure)	Drug exposure in surviving Rhesus monkeys compared to human plasma concentrations
	21721-SE1-003	Nov. 24, 2004	Treatment of inhalational anthrax (post-exposure)	Plasma concentrations

Drug name	NDA/BLA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
	20634-SE5-047	May 5, 2008	Treatment of inhalational anthrax (post-exposure) in pediatric patients (over 6 months of age) in certain circumstances	PK modeling in pediatric patients to extrapolate plasma concentration/exposure from adult data
	20635-SE5-051	May 5, 2008	Treatment of inhalational anthrax (post-exposure) in pediatric patients (over 6 months of age) in certain circumstances	PK modeling in pediatric patients to extrapolate plasma concentration/exposure from adult data
	21721-SE5-015	May 5, 2008	Treatment of inhalational anthrax (post-exposure) in pediatric patients (over 6 months of age) in certain circumstances	PK modeling in pediatric patients to extrapolate plasma concentration/exposure from adult data
Bexxar	125011-24[a]	Dec. 22, 2004	Treatment of relapsed or refractory, low grade, follicular or transformed CD20 positive non-Hodgkin's lymphoma in specific patients	Response rate[c]
Clolar	21673	Dec. 28, 2004	Treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens	Complete response rate and complete response without platelet recovery[c]
Aptivus	21814	June 22, 2005	Treatment of Human Immunodeficiency Virus-1 infection in specific adult patients under certain circumstances	Viral load (HIV-RNA)
Arranon	21877	Oct. 28, 2005	Treatment of T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma in specific patients	Complete response rate[c]
Exjade	21882	Nov. 2, 2005	Treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older	Lowering of liver iron content
Sutent	21968	Jan. 26, 2006	Treatment of advanced renal cell carcinoma	Response rate[c]
Thalomid	21430	May 25, 2006	Treatment of newly diagnosed multiple myeloma	Response rate (serum or urine paraprotein)[c]
Prezista	21976	June 23, 2006	Treatment of human immunodeficiency virus infection in specific patients	Viral load (HIV-RNA)
Sprycel	21986	June 28, 2006	Treatment of chronic myeloid leukemia with resistance or intolerance to prior therapy including imatinib in adults	Major cytogenic response
Vectibix	125147[a]	Sept. 27, 2006	Treatment of specific metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine oxaliplatin and irinotecan containing chemotherapy regimens	Progression-free survival
Selzentry	22128	Aug. 6, 2007	Treatment of CCR5-tropic Human Immunodeficiency Virus-1	Viral load (HIV-RNA)

Drug name	NDA/BLA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Isentress	22145	Oct. 12, 2007	Treatment of Human Immunodeficiency Virus infection in specific patients	Viral load (HIV-RNA)
Tasigna	22068	Oct. 29, 2007	Treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia in specific adult patients	Major cytogenic response and hematologic response
Intelence	22187	Jan. 18, 2008	Combination antiretroviral treatment for Human Immunodeficiency Virus-1 infection in specific patients	Viral load (HIV-RNA)
Avastin	125085-91[a]	Feb. 22, 2008	Treatment of breast cancer in specific patients	Progression-free survival
Promacta	22291	Nov. 20, 2008	Treatment of thrombocytopenia in specific patients	An increase from the baseline platelet count to a count greater than or equal to 50,000/mcL

Source: GAO analysis of FDA data.

[a]Applications for therapeutic BLAs. These therapeutic biologics were transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research on June 30, 2003.

[b]In addition to the surrogate endpoint used for approval, there was evidence of clinical benefit supporting the approval of this application.

[c]Response rate and complete response surrogate endpoints are tumor assessment endpoints which measure the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period.

Appendix II: Applications for Drugs Approved under FDA's Traditional Process Using Surrogate Endpoints

Between January 1998 and June 2008, the Food and Drug Administration (FDA) approved 204 New Molecular Entity (NME) drugs under its traditional process. Of those 204, 69 NME drugs were approved using surrogate endpoints. Table 6 provides a description of each of the 69 NME drugs, their new drug application (NDA) numbers, and the surrogate endpoints used for approval.

Table 6: NDAs Approved Based on Surrogate Endpoints under the Traditional Approval Process, from January 1, 1998–June 30, 2008

Drug name	NDA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Refludan	20807	Mar. 6, 1998	Anticoagulation treatment in patients with heparin-induced thrombocytopenia and thromboembolic disease	Time courses of platelets and activated partial thromboplastin time for regimen A1, A2, and B, and on the time course of Ecarin clotting time (ECT) for regimen C
Lotemax	20583	Mar. 9, 1998	Treatment of post-operative inflammation and uveitis[a]	Measurements of cell and flare and resolution of anterior chamber cell
Actonel	20835	Mar. 27, 1998	Treatment of Paget's disease of bone in specific patients	Serum alkaline phosphatase levels
Azopt	20816	April 1, 1998	Treatment of elevated intraocular pressure in specific patients	Intraocular pressure levels
Zemplar injection	20819	April 17, 1998	Prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure	Intact parathyroid hormone levels
Atacand	20838	June 4, 1998	Treatment of hypertension	Systolic and diastolic pressure levels
Vitravene	20961	Aug. 26, 1998	Treatment of cytomegalovirus retinitis in specific patients with Acquired Immunodeficiency Syndrome	Median time to cytomegalovirus retinitis progression
Valstar	20892	Sept. 25, 1998	Treatment of BCG -refractory carcinoma in situ of the urinary bladder in specific patients	Time to recurrence of disease after treatment compared to recurrence after previous courses of intravesical therapy
Renagel	20926	Oct. 30, 1998	Treatment of end-stage renal disease	Serum phosphorous levels
Micardis	20850	Nov. 10, 1998	Treatment of hypertension	Blood pressure levels
Ferrlecit	20955	Feb. 18, 1999	Treatment for iron deficiency in specific patients undergoing chronic hemodialysis	Hemoglobin levels
Avandia	21071	May 25, 1999	Treatment of type 2 diabetes mellitus	Blood sugar (fasting plasma glucose and HBA1c levels)
Hectorol	20862	June 9, 1999	Treatment of secondary hyperparathyroidism in specific patients	Intact parathyroid hormone levels

Drug name	NDA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Actos	21073	July 15, 1999	Treatment of type 2 diabetes mellitus	Blood sugar (fasting plasma glucose and HBA1c levels)
Aromasin	20753	Oct. 21, 1999	Treatment of advanced breast cancer in postmenopausal women	Objective response rate (partial and complete)[b]
Protonix	20987	Feb. 2, 2000	Treatment of erosive esophagitis associated with gastroesophageal reflux disease	Healing of lesions to grade 1 or 0 in the Hetzel-Dent scale
Lantus	21081	April 20, 2000	Treatment of type 1 diabetes mellitus in adults or pediatric patients or type 2 diabetes mellitus in specific adult patients	Blood sugar (glycated hemoglobin levels)
Welchol	21176	May 26, 2000	Treatment of elevated LDL cholesterol in specific patients	LDL cholesterol levels
NovoLog	20986	June 7, 2000	Treatment of diabetes mellitus in adult patients	Glycemic control, the rates of hypoglycemia, and the incidence of ketosis
Trelstar Depot	20715	June 15, 2000	Treatment of advanced prostate cancer	Achievement of castration by Day 29 and maintenance of castration levels of serum testosterone from Day 57 through Day 253
Rescula	21214	Aug. 3, 2000	Treatment of open-angle glaucoma or ocular hypertension	Intraocular pressure levels
Cetrotide	21197	Aug. 11, 2000	Treatment of premature luteinizing hormone surges in women undergoing controlled ovarian stimulation	Luteinizing hormone surge
Trisenox	21248	Sept. 25, 2000	Treatment of acute promyelocytic leukemia	Cytogenic conversion to no detection of the acute promyelocytic leukemia chromosome rearrangement
Starlix	21204	Dec. 22, 2000	Treatment of type 2 diabetes mellitus	Blood sugar (fasting plasma glucose and HBA1c levels)
Foradil Aerolizer	20831	Feb. 16, 2001	Treatment of asthma and prevention of bronchospasm	Forced expiratory volume in one second
Lumigan	21275	Mar. 16, 2001	Treatment of elevated intraocular pressure in certain populations	Intraocular pressure levels
Travatan	21257	Mar. 16, 2001	Treatment of intraocular pressure in certain populations	Intraocular pressure levels
Natrecor	20920	Aug. 10, 2001	Treatment of acute decompensated congestive heart failure in specific populations	Pulmonary capillary wedge pressure levels
Zometa	21223	Aug. 20, 2001	Treatment of hypercalcimia of malignancy	Complete response (lowering of the corrected serum calcium)[b]

Drug name	NDA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Benicar	21286	April 25, 2002	Treatment of hypertension	Peak and trough blood pressure levels
Faslodex	21344	April 25, 2002	Treatment of metastatic breast cancer	Response rate and time to progression[b]
Hepsera	21449	Sept. 20, 2002	Treatment of chronic hepatitis B	Knodell Necroinflammatory Score (i.e. liver biopsy)
Inspra	21437	Sept. 27, 2002	Treatment of hypertension	Sitting diastolic and systolic blood pressure at trough
Zetia	21445	Oct. 25, 2002	Treatment of elevated total cholesterol levels and LDL-C	Cholesterol levels
Extraneal	21321	Dec. 20, 2002	Single daily exchange for the long dwell during continuous ambulatory peritoneal dialysis or automated peritoneal dialysis for the treatment of chronic renal failure	Ultrafiltration rate
Somavert	21106	Mar. 25, 2003	Treatment of acromegaly in specific patients	Serum IGF-I levels
Reyataz	21567	June 20, 2003	Treatment of Human Immunodeficiency Virus-1 infection	CD4 count (infection fighting white blood cell) and viral load (HIV-RNA)
Emtriva	21500	July 2, 2003	Treatment of Human Immunodeficiency Virus-1 infection in adults	CD4 count (infection fighting white blood cell) and viral load (HIV-RNA)
Zavesca	21348	July 31, 2003	Treatment of mild to moderate type 1 Gaucher disease	Liver and spleen volume after 12 months of treatment
Crestor	21366	Aug. 12, 2003	Treatment of cholesterol levels	Cholesterol levels
Radiogardase	21626	Oct. 2, 2003	Treatment of internal contamination with radioactive cesium and/or radioactive thallium	Whole body effective half life of cesium or thallium
Plenaxis	21320	Nov. 25, 2003	Palliative treatment for men with advanced symptomatic prostate cancer for specific reasons	Avoid orchiectomy and lower serum testosterone levels
Spiriva Handihaler	21395	Jan. 30, 2004	Treatment of bronchospasm associated with chronic obstructive pulmonary disease	Forced expiratory volume in one second, with peak effect occurring within 3 hours following the first dose
Sensipar	21688	Mar. 8, 2004	Treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis	Intact parathyroid hormone levels
Apidra	21629	April 16, 2004	Treatment of diabetes mellitus in adult patients	Blood sugar (glycated hemoglobin and HbA1c equivalents)

Drug name	NDA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Vidaza	50794	May 19, 2004	Treatment of myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia	Response rate[b]
Pentetate Calcium Trisodium	21749	Aug. 11, 2004	Treatment of known or suspected internal contamination with plutonium, americium, or curium to increase rates of elimination	Ratio of urine radioactivity before treatment to the maximum urine radioactivity after treatment (excretion enhancement factor)
Pentetate Zinc Trisodium	21751	Aug.11, 2004	Treatment of known or suspected internal contamination with plutonium, americium, or curium to increase rates of elimination	Ratio of urine radioactivity before treatment to the maximum urine radioactivity after treatment (excretion enhancement factor)
Fosrenol	21468	Oct. 26, 2004	Treatment of end stage renal disease	Serum phosphate levels
Omacor[c]	21654	Nov. 10, 2004	Treatment of very high triglyceride levels in adults	Triglyceride levels
Symlin	21332	Mar. 16, 2005	Treatment of type 1 or type 2 diabetes mellitus	Blood sugar (HbA1c levels)
Mycamine	21506	Mar. 16, 2005	Treatment of esophageal candidiasis or prophalaxis against fungal infection	Endoscopic appearance of the esopageal mucosa
Baraclude	21797	Mar. 29, 2005	Treatment of chronic hepatitis B in adults	Knodell Necroinflammatory Score (i.e. liver biopsy)
Byetta	21773	April 28, 2005	Treatment of type 2 diabetes mellitus	Blood sugar (HbA1c levels)
Levemir	21536	June 16, 2005	Treatment of diabetes mellitus in adults who require basal insulin for control of hyperglycemia	Blood sugar (fasting blood glucose and HBA1c levels)
Nexavar	21923	Dec. 20, 2005	Treatment of advanced renal cell carcinoma	Progression free survival
Vaprisol	21697	Dec. 29, 2005	Treatment of euyolemic hyponatremia in hospitalized patients	Serum sodium concentration levels
Sutent	21938	Jan. 26, 2006	Treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma	Time to progression
Pylera	50786	Sept. 28, 2006	Treatment of helicobacter pylori infection and duodenal ulcer disease	C-urea breath tests
Januvia	21995	Oct. 16, 2006	Treatment of type 2 diabetes mellitus	Blood sugar (fasting blood glucose, HBA1c levels and post prandial glucose)
Tyzeka	22011	Oct. 25, 2006	Treatment of chronic hepatitis B in specific populations of adults	Composite serologic endpoint requiring suppression of HBV DNA to a specific amount in conjunction with another serum

Drug name	NDA number	Approval date	Approved indication	Surrogate endpoint(s) used to approve application
Tekturna	21985	Mar. 5, 2007	Treatment of hypertension	Seated trough cuff blood pressure
Tykerb	22059	Mar. 13, 2007	Treatment of advanced metastatic breast cancer	Time to progression
Somatuline Depot	22074	Aug. 30, 2007	Treatment of acromegalic patients who have inadequate response to surgery and/or radiotherapy	Growth hormone and insulin growth factor levels
Ixempra	22065	Oct. 16, 2007	Treatment of metastatic or locally advanced breast cancer	Progression free survival
Kuvan	22181	Dec. 13, 2007	Treatment of hyperphenylalaninemia	Blood phenylalanine levels
Bystolic	21742	Dec. 17, 2007	Treatment of hypertension	Trough sitting systolic/diastolic blood pressure
Treanda	22249	Mar. 20, 2008	Treatment of chronic lymphocytic leukemia	Objective response and progression-free survival[b]
Durezol	22212	June 23, 2008	Treatment of inflammation and pain in the eye associated with ocular surgery	Complete clearing (count = 0)

Source: GAO analysis of FDA data.

[a]Also approved for treatment of giant papillary conjunctivitis and seasonal allergic conjunctivitis. However, these indications were approved based on clinical endpoints and are not included in the table.

[b]Response rate is a measure of the proportion of patients with tumor size reduction of a predefined amount and for a minimum time period.

[c]In July 2007, the name of this drug was changed from Omacor to Lovaza.

Appendix III: Applications Selected and Questions Regarding FDA's Oversight of Required Postmarketing Studies

To review specific instances of the Food and Drug Administration's (FDA) monitoring and enforcement activities, we selected a judgmental sample of 15 applications approved based on surrogate endpoints under the accelerated program and the 35 postmarketing studies that FDA required drug sponsors to complete for these drugs. These applications were selected to generate a sample that included a variety of drugs and a range of studies at various stages of completion. We then provided FDA with a standard series of questions for each of the 35 studies, and requested that FDA's medical reviewers, who are responsible for monitoring these 35 studies, provide specific information on them, including a description of the studies, FDA's efforts to monitor these studies, and applicable enforcement actions taken, if any, to prompt sponsors' compliance. FDA officials indicated that several individuals were involved in completing the questions provided for each of the 15 applications. FDA staff completed the first half of the questions related to description of the studies. The medical reviewers or other review staff provided information on the agency's monitoring efforts and enforcement actions. The applications we selected and the information request are provided below.

Table 7: List of 15 Accelerated Approval Applications Selected for Review

Drug name	NDA/BLA number	Approval date
ProAmatine	19815	Sept. 6, 1996
Xeloda	20896	April 30, 1998
Sulfamylon	19832	June 5, 1998
Priftin	21024	June 22, 1998
Remicade	103772	Aug. 24, 1998
Viramune	20933	Sept. 11, 1998
Sustiva	20972	Sept. 17, 1998
Ziagen	20977	Dec. 17, 1998
Celebrex	21156	Dec. 23, 1999
Gleevec	21588	April 18, 2003
Zevalin	125019	Feb. 19, 2002
Fuzeon	21481	Mar. 13, 2003
Fabrazyme	103979	April 24, 2003
Iressa	21399	May 5, 2003
Velcade	21602	May 13, 2003

Source: GAO analysis of FDA data.

Information Request on the Monitoring and Oversight of Drugs Approved Based on Surrogate Endpoints

Instructions: Please review the pre-filled information and provide information on your monitoring of the drug sponsor's completion of postmarketing study (ies) required under the accelerated approval program. When you have completed this request, please return it to GAO via email at Lichtenfeldd@GAO.gov. Please contact David Lichtenfeld at (312) 220-7663 if you have any questions.

NDA Number:

Approval Date:

Drug Name:

Division:

Number of required studies:

Commitment IDs and Status:

Source: FDA-provided data on required postmarketing commitments (as of December 19, 2008)

For study # please provide answers to the following questions:

1. What is the study description as outlined in the approval letter or annual status report (ASR)?
2. Was there ever an original study schedule or timeline established for this study? If yes, when was it established and how was it documented (e.g. in approval letter, first ASR etc.)?
3. If a study schedule was not established, how have you determined the current status of the study?
4. When was this study assigned its current status?
5. Has/did the drug sponsor submit all required ASRs for this study, and were they submitted within required timeframes?
6. If the sponsor did not submit all required ASRs in a timely manner, what action(s) did FDA take to obtain the sponsor's compliance (e.g., initiate a teleconference, issue administrative letter)?
   Please provide any available documentation demonstrating FDA's effort to follow-up with the drug sponsor regarding ASR submissions for this study.
7. Has FDA reviewed all of the ASRs submitted for this study, and have they been reviewed within FDA review timeframes—within 90 days of receipt?
8. If FDA has not reviewed all of the ASRs according to its policy, what barriers have prevented FDA from conducting these reviews? In addition, when will FDA complete its reviews of any outstanding ASRs for this study?

9. Based on its review of ASRs submitted for this study, has FDA identified any problems or concerns with the drug sponsor's progress in completing this study? For example, did FDA's reviews reveal that the study had been either pending or delayed for an extended period of time, or did its reviews provide indications that the sponsor would not be able to complete the study within established timeframes? If so, what actions did FDA take to compel the sponsor to complete the study?
Please provide any available documentation demonstrating FDA's efforts to follow-up with the sponsor regarding progress for this study.

10. Based on its review of ASRs submitted for this study, has FDA identified any significant underlying issues affecting the sponsor's ability to complete this study? For example, did the sponsor experience any problems designing the study or enrolling patients that affected the progress of the study? If so, what actions did FDA take to help the sponsor improve the progress of the study?
Please provide any available documentation demonstrating FDA's efforts to follow-up with the sponsor regarding this study's completion.

11. Outside of ASR reviews, has FDA used any other mechanisms to monitor the progress of this study (e.g. routine conference calls or other routine communication with the sponsor)?

12. If the status of this study is fulfilled, what factors contributed to the completion of the study?

13. Please provide any additional comments you believe are relevant to the oversight and monitoring of this study.

Name of FDA Reviewer Who Answered these Questions:

How long has the Reviewer been responsible for monitoring this study: (Please check the appropriate box.)

☐ 1-2 years ☐ 3-4 years ☐ 5-6 years ☐ 7-8 years ☐ 9-10 years ☐ over 10 years

Appendix IV: Sales for Selected Drugs Approved Based on Surrogate Endpoints under the Accelerated Approval Process

Listed in table 8 are seven applications for drugs approved based on surrogate endpoints under the accelerated approval process, and total U.S. sales, since approval, associated with those drugs. This listing includes applications, which as of December 19, 2008, had not been converted to full approval, and more than 5 years had elapsed since they were initially approved.

Table 8: Total U.S. Sales for Selected Drugs Approved under the Accelerated Process

Application type	Application number	Drug name	Approval date	Total U.S. sales since approval[a]
NDA	19815	ProAmatine	Sept. 6, 1996	$257,574,554
NDA	19832	Sulfamylon	June 5, 1998	$72,963,020[b]
NDA	21024[c]	Priftin	June 22, 1998	$177,502
NDA	50747	Synercid	Sept. 21, 1999	$206,741,816
NDA	21174	Mylotarg	May 17, 2000	$206,982,392
NDA	21399	Iressa	May 5, 2003	$416,699,000
BLA	103979	Fabrazyme	April 24, 2003	$56,308,877

Source: GAO analysis of FDA data and National Sales Perspectives (™) IMS Health, Inc.

[a]Sales data through December 2008.

[b]Annual sales since 1998 for Sulfamylon include sales for this approval and an earlier approval, which occurred prior to the implementation of the accelerated approval process.

[c]The Food and Drug Administration converted the application for Priftin to full approval on June 1, 2009.

Appendix V: 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

SEP 8 2009

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

Dear Ms. Crosse:

Enclosed are comments on the U.S. Government Accountability Office's (GAO) report entitled: NEW DRUG APPROVAL: FDA Needs to Enhance its Oversight of Drugs Approved on the Basis of Surrogate Endpoints (GAO-09-866).

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

Sincerely,

Andrea Palm
Acting Assistant Secretary for Legislation

Enclosure

FDA's General Comments to the United States Government Accountability Office's Draft Report Entitled, *New Drug Approval: FDA Needs to Enhance its Oversight of Drugs Approved on the Basis of Surrogate Endpoints* (GAO-09-866)

The Food and Drug Administration (FDA) welcomes the opportunity to comment on the Government Accountability Office's (GAO) findings in the draft report and respond to the single recommendation made by GAO to FDA.

FDA believes that the accelerated approval program has been very successful. It has resulted in the early approval of many significant therapeutic advances for patients with serious or life-threatening illnesses who desperately need access to new treatments, in some cases years before the drug would have been available under regular approval procedures. For patients with HIV/AIDS and cancer, especially, the accelerated approval program has dramatically expanded the therapeutic armamentarium and significantly improved their quality of life and survival.

By focusing primarily on the limited number of cases where the postmarketing trials to confirm clinical benefit either have taken longer to complete than expected or have not demonstrated clinical benefit in the manner that had been anticipated, GAO's report minimizes the fact that, as reflected in GAO's own analysis, overall the accelerated approval program functions precisely as intended and designed. First, through the accelerated approval program, millions of patients with serious or life-threatening illnesses have had earlier access to new safe and effective treatments. Second, in the vast majority of cases, the confirmatory trials have been or are being completed in a timely manner, have confirmed clinical benefit, and have led to conversion to regular approval. These findings are important for patients and also provide validation of the underlying public health principles of the accelerated approval program.

FDA developed the accelerated approval program with full recognition of the risk that drugs might be approved and later found not to confer clinical benefit to patients. After much input from stakeholders, FDA determined that this was a risk worth taking because patients with serious or life-threatening illnesses and their physicians are willing to accept more risk when making treatment decisions. FDA also sought to minimize the risk that patients would be exposed to approved treatments that were not safe and effective by incorporating four important safeguards into the program. First, the evidentiary standard for accelerated approval and regular approval is the same, meaning that there must be substantial evidence that the drug has the purported effect on the surrogate endpoint and there must be adequate safety data for FDA to conclude that the benefits of the drug outweigh the risks. Second, the surrogate endpoint must be considered reasonably likely to predict clinical benefit. Third, clinical trials to confirm clinical benefit are required after approval and must be completed with due diligence by the sponsor. Finally, FDA can undertake expedited withdrawal procedures if clinical benefit is not confirmed.

The facts as outlined in GAO's report show that the surrogate endpoints used as the basis for accelerated approval have, in most cases, served as accurate predictors of clinical

benefit. This is demonstrated by the fact that two thirds of the required confirmatory studies are now considered closed by FDA and over half of the drugs approved under accelerated approval have been converted to regular approval. FDA's oversight of this program, including careful selection of surrogates and extensive efforts to work closely with sponsors to design and ensure timely completion of confirmatory trials, has served to make it a success.

FDA has previously acknowledged that its oversight of postmarketing requirements (PMR) and commitments (PMC) in general has been inadequate; however oversight of postmarketing trials of drugs approved under accelerated approval has always been an important FDA priority. As noted above, nearly two thirds of the required confirmatory trials are now considered complete by FDA. This is clear evidence that both FDA and sponsors have taken their postmarketing obligations under this program seriously.

With regard to oversight of the much larger overall portfolio of PMRs and PMCs, FDA agrees that improvements are needed. In the past, because of inadequate staffing and information technology resources and competing workload priorities, the Center for Drug Evaluation and Research (CDER) has been unable to thoroughly track PMRs and PMCs or to review annual status reports and final study reports in a timely fashion. With increased resources from Congressional appropriations and statutory requirements, CDER has begun to implement a number of process improvements to ensure appropriate oversight, more efficient tracking, and expeditious review of postmarketing submissions. These improvements were not complete at the time of this GAO investigation and are not fully reflected by the data included in the report. These efforts include the following:

- Publication of a new PMR/PMC Development Manual of Policies and Procedures (MAPP) and significant revision of the PMR/PMC Tracking MAPP;
- Establishment of the new roles of PMR/PMC Development and Tracking Coordinators within each new drug review division;
- Implementation of new PMR/PMC functions in the document archiving and records retention system database (DARRTS), which will improve PMR/PMC tracking by enhancing FDA's ability to capture data and generate reports; and
- Contracting with Booz Allen Hamilton (BAH) to assist FDA staff with the review of annual status reports and to conduct an independent review of the backlog of all open PMRs and PMCs.

BAH's audit has led to extensive updates to the data in FDA's tracking database and revealed that most of the industry postmarketing studies and trials are proceeding according to the agreed-upon timeline. FDA plans to continue its contract with BAH to ensure that the new processes are implemented and the data in the database are accurate and up-to-date going forward. FDA also plans to make the BAH audit report available to the public.

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Response to GAO's Recommendation

GAO recommended that to clarify FDA's enforcement authority under the accelerated approval process, the Commissioner of FDA take the following action: Clarify the conditions under which the agency would utilize its authority to expedite the withdrawal of drugs approved based on surrogate endpoints under the accelerated approval process if sponsors fail to complete required confirmatory studies with due diligence, or if studies are completed, but fail to demonstrate the clinical effectiveness of the drugs.

FDA acknowledges that there have been cases where confirmation of the clinical benefit of drugs approved under accelerated approval did not occur in a timely manner. FDA considers the lack of progress or completion of confirmatory trials seriously and works closely with sponsors to get the required trials back on track for completion. In some cases it has been difficult to design or successfully enroll patients in the confirmatory trials and FDA and sponsors have worked together to find acceptable solutions, including alternate trial designs or expanding enrollment to international sites. FDA also has conducted public reviews of outstanding confirmatory trials for oncology drugs to focus attention on the delays and to seek advice from its advisory committee experts on ways to get the necessary trials completed.

When trials are not being completed in a timely manner or completed trials do not appear to confirm clinical benefit, FDA must carefully assess each case and consider the underlying reasons and the consequences of all regulatory options, including their potential impact on patients. The fact that a trial has not been completed in what appears to be a timely manner can reflect the failure of a sponsor to exercise due diligence in the conduct of the trial, but it can also reflect, for example, difficulty in identifying and enrolling appropriate patients. Failure to confirm clinical benefit in a completed trial may reflect the possibility that the drug does not in fact confer clinical benefit, but it also may reflect, for example, unforeseen limitations in trial design, rather than clear evidence of lack of effectiveness. The most appropriate regulatory approach must be governed by the unique factors of the particular case.

By definition, drugs approved under accelerated approval represent significant therapeutic advances for patients with serious and life-threatening illnesses. FDA must carefully evaluate what other options are available to patients at the time it is considering regulatory action for failure to confirm clinical benefit. In some cases a drug for which clinical benefit has not been confirmed may be the only approved therapeutic option for patients with the disease. Removing the drug from the market and leaving patients with no treatment may be unacceptable. In such a case FDA must consider the benefits of continued availability of the drug, which by definition under the accelerated approval program was shown to have an effect on the surrogate endpoint that was the basis for approval, versus the risk that patients may actually be using an ineffective drug and exposing themselves only to its risks. FDA must also consider the possibility that, despite results from confirmatory studies that may appear to indicate that a drug does not

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provide clinical benefit, there may be a subset of patients for whom the drug may nevertheless be effective. Further, in addition to withdrawal of approval, FDA has other regulatory tools that can be considered and applied as appropriate. These include requiring a Risk Evaluation and Mitigation Strategy (REMS) under the new authority granted to FDA in the Food and Drug Administration Amendments Act of 2009 (FDAAA) or limiting access to the drug under an Investigational New Drug application (IND).

Two specific drugs were mentioned in the report and warrant comment:

ProAmatine (midodrine hydrochloride) was approved by FDA as a treatment for patients with orthostatic hypotension, a condition in which a patient's blood pressure decreases upon standing, which can lead to syncope (fainting) and falls. Orthostatic hypotension is a serious disabling condition and there are no other FDA approved drugs for this condition. The surrogate endpoint used for approval was an increase in systolic blood pressure on standing. Although FDA routinely uses blood pressure as a validated surrogate endpoint for the treatment of hypertension, in the case of ProAmatine, FDA faced the opposite situation, i.e., a drug intended to *increase* blood pressure in patients with hypotension. Here FDA was not certain that the observed increase in systolic blood pressure would lead to clinical benefit, and the sponsor was required to conduct postapproval clinical trials to assess relevant clinical endpoints (e.g., decrease in symptoms).

The sponsor conducted postapproval trials as required, and while FDA did not consider the trials adequate to confirm clinical benefit, there were trends observed that suggested the drug may in fact have clinical benefit. Since this drug is the only approved therapy for this condition, FDA has not concluded that it would be appropriate to initiate expedited withdrawal of the approval. We note that the ProAmatine case is complicated by the fact that there are approved generic versions of the product. FDA has worked through complex legal and regulatory issues to find ways to encourage one or more of the generic sponsors to conduct the necessary clinical trials. FDA is continuing to evaluate options in this case.

Rather than an example of FDA failing to exercise its authority to withdraw approval, ProAmatine is a good example of the complex issues FDA must consider when clinical benefit has not been confirmed and the drug approved under accelerated approval remains the only FDA-approved treatment for a serious or life-threatening condition. FDA must carefully balance exercising its regulatory authority versus considering the best interests of patients with the disease or condition.

The second drug mentioned in the GAO report is Iressa (gefitinib). Iressa was approved by FDA as a treatment for patients with advanced non-small cell lung cancer, a serious and life-threatening form of cancer for which there were few treatment options at the time Iressa was approved. The sponsor conducted a large, randomized, controlled clinical trial in over 1700 patients with less advanced lung cancer and the trial failed to show an improvement in survival time for patients treated with Iressa; i.e., clinical benefit was not

confirmed. By the time the postmarketing trial results for Iressa were available; another similar drug (Tarceva) had been approved and had demonstrated an increase in survival time in patients with non-small cell lung cancer.

In considering this case, FDA noted that while the controlled clinical trial failed to show a survival benefit for the overall study population, there was clear evidence in individual patients of significant clinical benefit (e.g., shrinkage of large tumors and prolonged survival in patients with end-stage disease) that could not be ascribed to factors other than drug effect. There was also a suggestion, though not yet proven by controlled clinical trials, that certain patients might be responsive to Iressa due to the genetic markers on their tumor cells while other patients might not respond. This was thought to possibly explain the dramatic individual responses seen in some patients and the lack of response seen in others. This could also explain the failure to see a clinical benefit in a mixed population of patients, many of whom might not be responsive to Iressa due to the genetic makeup of their tumors.

After considering all the available information, FDA believed that it was appropriate to direct patients beginning treatment for non-small cell lung cancer to treatment with Tarceva, because clinical benefit in the form of a survival advantage had been confirmed. FDA also believed that patients who were already being treated with Iressa and in whom a clinical response was observed might appropriately choose, after consultation with their doctors, to remain on Iressa. Rather than withdraw approval of Iressa, FDA worked with the sponsor to restrict access to those patients who were already receiving treatment and whose physician felt were deriving clinical benefit from the drug. Since marketing of Iressa was restricted, patients with other diseases whose physicians might have prescribed the drug for those different indications were accommodated through access under an Investigational New Drug Application.

FDA believes that this combination of regulatory actions was an appropriate and balanced approach given the unique circumstances in this case. The sponsor of Iressa has continued to investigate the factors that might predict response to the drug, and it is possible that future clinical trials in properly selected patients will demonstrate clinical benefit.

In both of these examples, the sponsors pursued confirmatory clinical trials with due diligence, but despite careful consideration and review by both industry and the FDA, the trials did not demonstrate clinical benefit. In both cases, review of the data suggests limitations in elements of trial design that may have led to the seemingly negative results.

GAO recommends that FDA "[c]larify the conditions under which the agency would utilize its authority to expedite the withdrawal of drugs approved based on surrogate endpoints under the accelerated approval process if sponsors either fail to complete required confirmatory trials with due diligence, or if studies are completed, but fail to demonstrate the clinical effectiveness of the drugs." Outside of a situation where a confirmatory trial clearly demonstrates harm to the patients (e.g., decreased survival for patients with cancer treated with the accelerated approval drug), FDA believes that each

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case must be considered on its merits and that the criteria in the existing regulations and statutory provisions (including the provisions in Title IX of FDAAA that authorize civil, criminal, and civil monetary penalties for failure to conduct a postmarketing confirmatory trial) provide FDA with sufficient authority and flexibility to make balanced decisions that protect the program from abuse by sponsors and ensure that patients will continue to have access to needed treatments. In light of the complexities outlined above and the need for a case-by-case assessment, FDA believes it would be difficult, if not impossible, to provide further clarification as to when it might utilize its authority to expedite withdrawal of drug approved on the basis of surrogate endpoints. FDA remains committed to closely overseeing required postmarketing trials for drugs approved under accelerated approval and believes that the improvements being implemented in its overall PMR/PMC program will allow for continued success of the program.

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Appendix VI: GAO Contact and Staff Acknowledgments

GAO Contact

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