



Report to the Ranking Member,
Subcommittee on Labor, Health and
Human Services, Education, and Related
Agencies, Committee on Appropriations,
House of Representatives

December 2015

DRUG SAFETY

FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement

Accessible Version

GAO Highlights

Highlights of [GAO-16-192](#), a report to the Ranking Member, Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, Committee on Appropriations, House of Representatives

Why GAO Did This Study

FDA oversees the safety and effectiveness of drugs sold on the U.S. market. When there is an unmet need for the treatment of a serious condition, FDA may use one or more of its expedited programs, such as fast track and breakthrough therapy designation, which are intended to bring drugs to market more quickly. FDA is also responsible for monitoring the safety of drugs and reporting on those efforts.

GAO was asked to provide information about FDA's expedited programs and its postmarket monitoring of expedited and nonexpedited drugs. This report examines (1) the number and types of requests for fast track or breakthrough therapy designation, (2) the number and types of FDA-approved drug applications that used an expedited program, and (3) the extent to which FDA's data on tracked safety issues and postmarket studies allowed the agency to meet its reporting and oversight responsibilities. GAO analyzed FDA data on requests for fast track or breakthrough therapy designation and approved drug applications that used an expedited program from October 1, 2006, to December 31, 2014 (the most recent available). GAO reviewed FDA information on tracked safety issues and postmarket studies, including FDA internal evaluations and guidance, and interviewed FDA officials.

What GAO Recommends

FDA should develop plans to correct problems with its postmarket safety data and ensure that these data can be easily used for oversight. HHS agreed with GAO's recommendations and provided additional information on FDA's postmarket safety efforts.

View [GAO-16-192](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

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FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement

What GAO Found

From October 1, 2006, to December 31, 2014, the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research (CDER) received about 1,000 requests for fast track designation and breakthrough therapy designation—two of the agency's four expedited programs to facilitate and expedite the development and review of new drugs. Drug sponsors are required to submit formal requests to use these two programs; for the other two expedited programs (accelerated approval and priority review) sponsors are not required to submit formal requests. Regardless of whether sponsors submit a request for an expedited program, they are required to submit a marketing application prior to offering a drug for sale in the United States; using an expedited program does not ensure FDA approval of the marketing application. Sponsors submitted more than 770 requests for fast track designation since fiscal year 2007, and FDA granted about two-thirds of these requests. Sponsors submitted more than 220 requests for breakthrough therapy designation since it was established in July 2012, and the agency denied more than half of these requests.

About a quarter of the drug applications CDER approved for the U.S. market from October 1, 2006, to December 31, 2014, used at least one expedited program, according to FDA data. Included among these applications were new drug applications, biologic license applications, and efficacy supplements, which allow for revisions to the original application, such as changes in the drug's indicated use. Although most of these applications used one program, some applications used two or more, including two oncology drug applications that used all four expedited programs (accelerated approval, breakthrough therapy designation, fast track designation, and priority review). The most common product area among these applications was oncology (19 percent).

FDA lacks reliable, readily accessible data on tracked safety issues and postmarket studies needed to meet certain postmarket safety reporting responsibilities and to conduct systematic oversight. Tracked safety issues are potential safety issues that FDA determines are significant and that it tracks using an internal database. Internal control standards for federal agencies specify that information should be recorded in a form and within a time frame that enables staff to carry out their responsibilities and that relevant, reliable, and timely information should be available for external reporting purposes. However, evaluations conducted by CDER of data in its database revealed problems with the completeness, timeliness, and accuracy of the data. These problems, as well as problems with the way data are recorded that impair their accessibility, have prevented FDA from publishing statutorily required reports on certain potential safety issues and postmarket studies in a timely manner, and have restricted the agency's ability to perform systematic oversight of postmarket drug safety. Although FDA has taken some steps to address the problems with its data, the agency lacks plans that comprehensively outline its efforts and establish related goals and time frames. Additionally, FDA does not have plans to use these data to inform its oversight of its expedited programs, such as determining if drugs that used an expedited program were subsequently associated with tracked safety issues at rates or of types that differed from drugs that used FDA's standard process.

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Abbreviations

BLA	biologic license application
CDER	Center for Drug Evaluation and Research
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
HHS	Department of Health and Human Services
NDA	new drug application
NME	new molecular entity

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December 15, 2015

The Honorable Rosa L. DeLauro
Ranking Member
Subcommittee on Labor, Health and Human Services,
Education, and Related Agencies
Committee on Appropriations
House of Representatives

Dear Ms. DeLauro:

The Food and Drug Administration (FDA)—an agency within the Department of Health and Human Services (HHS)—is responsible for overseeing the safety and effectiveness of drugs sold in the United States.¹ Before a drug can be marketed, it must be approved by FDA, which evaluates a drug application to determine whether the new drug is safe and effective for its intended use. While FDA reviews most drug applications using its standard review process, the agency may also utilize one or more of its expedited programs—programs to facilitate and expedite the development and review of new drugs—for drugs that have the potential to address an unmet medical need for the treatment of serious conditions. Although they do not guarantee approval of a marketing application, FDA’s expedited programs—accelerated approval, breakthrough therapy designation, fast track designation, and priority review—are intended to reduce the development or review time needed to bring a drug to market. For example, expedited programs may allow for the approval of drugs based on fewer, smaller, or shorter clinical trials. FDA has expressed support for proposals to further streamline the review of certain kinds of drugs, such as antibiotics.² However, some patient advocates and researchers have raised questions about whether such efforts could expose patients to drugs that have not been adequately

¹Within FDA, the Center for Drug Evaluation and Research is responsible for overseeing the safety and effectiveness of drugs sold in the United States.

²Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, *21st Century Cures: Modernizing Clinical Trials and Incorporating the Patient Perspective – Dr. Woodcock*, testimony before the House Subcommittee on Health, Committee on Energy and Commerce, 113th Cong., 2nd sess., July 11, 2014.

tested and increase the potential for previously unrecognized safety issues to appear once those drugs are more widely used.³

Once FDA approves a drug for marketing, whether using an expedited program or not, the agency continues to monitor the drug's safety and is required by law to publicly report on certain aspects of the agency's postmarket safety efforts.⁴ For example, FDA identifies and evaluates potential safety issues with marketed drugs, and those that are considered significant are formally tracked in FDA's internal database and referred to as tracked safety issues. FDA also monitors drug sponsors' progress in completing postmarket studies—studies that are conducted after the drug is approved that provide information about a drug's safety, efficacy, or optimal use—that FDA has required or the sponsor has agreed to conduct.⁵ However, we and others have found weaknesses in FDA's oversight of postmarket safety for drugs in the past,⁶ such as the agency's lack of reliable information to determine the progress of postmarket studies. FDA's use of certain expedited programs to reduce the development time before a drug is approved further increases the importance of the agency's postmarket safety oversight, including the

³See, for example, Jonathan J. Darrow, et al., "New FDA Breakthrough-Drug Category – Implications for Patients," *New England Journal of Medicine*, vol. 370, no. 13 (2014) and T.J. Moore and C.D. Furberg, "The Safety Risks of Innovation: The FDA's Expedited Drug Development Pathway," *Journal of the American Medical Association*, vol. 308, no. 9 (2012).

⁴21 U.S.C. §§ 355(k)(5)(A), 356b(c).

⁵For this report, we use the term postmarket studies to refer to the studies and trials that FDA requires drug sponsors to conduct (known as postmarketing requirements) and those that FDA requests and drug sponsors agree to conduct (known as postmarketing commitments). FDA is required by law to publish reports on certain potential safety issues and postmarket studies; these reports help to inform external stakeholders about emerging safety issues and the agency's response to them, and whether drug sponsors are completing postmarket studies according to established time frames. 21 U.S.C. §§ 355(k), 356b(c).

⁶See, for example, GAO, *Drug Safety: Improvement Needed in FDA's Postmarket Decision-making and Oversight Process*, [GAO-06-402](#) (Washington, D.C.: Mar. 31, 2006); A. Baci, K. Stratton, and S. P. Burke, eds., Institute of Medicine of the National Academies, Committee on the Assessment of the U.S. Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Washington, D.C.: Sept. 22, 2006); and GAO, *Drug Safety: FDA Has Begun Efforts to Enhance Postmarket Safety, but Additional Actions Are Needed*, [GAO-10-68](#) (Washington, D.C.: Nov. 9, 2009).

extent to which it is monitoring for unforeseen problems once a drug is on the market.⁷

You asked us to provide information about FDA's use of expedited programs and how FDA monitors the safety of expedited and non-expedited drugs following approval for the U.S. market.⁸ This report examines

1. the number and types of requests for fast track or breakthrough therapy designation,
2. the number and types of drug applications that FDA approved for marketing that used one or more expedited programs, and
3. the extent to which FDA's data on tracked safety issues and postmarket studies allowed the agency to meet its reporting and oversight responsibilities.

To examine the number and types of requests for fast track or breakthrough therapy designation, we requested and analyzed data from FDA for these two expedited programs. We focused on the fast track and breakthrough therapy designation programs because drug sponsors are required to submit formal requests to use these two programs; for the other two expedited programs (accelerated approval and priority review) sponsors are not required to submit formal requests.⁹ Specifically, we reviewed FDA data on requests for fast track designation and breakthrough therapy designation, and the number of these requests that FDA granted or denied or that were withdrawn by the sponsor. The

⁷For example, see Bo Wang and Aaron S. Kesselheim, "Characteristics of Efficacy Evidence Supporting Approval of Supplemental Indications for Prescription Drugs in United States, 2005–14: Systematic Review," *British Medical Journal* (2015), and Chul Kim and Vinay Prasad, "Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of U.S. Food and Drug Administration Approvals," *Journal of the American Medical Association Internal Medicine* (2015), accessed October 27, 2015, <http://archinte.jamanetwork.com/article.aspx?articleid=2463590>.

⁸We also issued a separate report describing postmarket studies for medical devices. See GAO, *Medical Devices: FDA Ordered Postmarket Studies to Better Understand Safety Issues, and Many Studies Are Ongoing*, GAO-15-815 (Washington, D.C.: Sept. 30, 2015).

⁹As previously mentioned, irrespective of their use of expedited programs, sponsors are required to submit a marketing application to FDA before a drug can be approved for marketing in the United States.

requests we analyzed were for fast track designation that were received and reviewed by FDA's Center for Drug Evaluation and Research (CDER) from fiscal year 2007 through the first quarter of fiscal year 2015 (the most recent quarter for which data were available at the time of our review), and for breakthrough therapy designation from July 9, 2012, (the date this program was established) through December 31, 2014.¹⁰ The status of the request for fast track or breakthrough therapy designation—such as whether FDA granted or denied the request or if the request was withdrawn by the sponsor—is as of the date that FDA extracted the data we requested.¹¹ We report data on sponsors' requests for and FDA's decisions about fast track and breakthrough therapy designation by the fiscal year in which the request was made, even if FDA's decision to grant or deny the designation occurred in a subsequent fiscal year. In addition to analyzing the number of requests and the status of FDA's decisions on those requests, we also examined the extent to which requests were granted by FDA product category, which generally corresponds to the FDA review division (e.g., oncology or psychiatry drugs). Requests for fast track and breakthrough therapy designations are generally made before sponsors submit their applications for approval to market a drug, and FDA's decision to grant such a designation does not guarantee that FDA will subsequently approve the application for marketing.

To examine the number and type of drug applications that FDA approved for marketing that used one or more expedited programs, we requested and analyzed data from FDA on all new drug applications (NDA), biologic license applications (BLA), and NDA- and BLA-related efficacy supplements that FDA approved from fiscal year 2007 through the first

¹⁰For our analysis, we included all requests for fast track and breakthrough designation, including requests associated with investigational new drug applications and with other drug applications, such as new drug applications. A sponsor must submit an investigational new drug application that summarizes the data that have been collected on the compound and outlines plans for the clinical trials. According to FDA officials, fast track and breakthrough therapy designation may be granted for an investigational new drug or later, such as when a new drug application is submitted. The Food and Drug Administration Safety and Innovation Act, signed into law in 2012, required FDA to establish breakthrough therapy designation. Pub. L. No. 112-144, § 902, 126 Stat. 993, 1086 (2012) (amending the Federal Food, Drug, and Cosmetic Act § 506; codified at 21 U.S.C. § 356).

¹¹FDA extracted data from its database for fast track designation in two rounds—fast track data through September 30, 2010, were extracted on May 31, 2015, and fast track data after September 30, 2010, were extracted on June 2, 2015. FDA extracted data for breakthrough therapy designation on April 30, 2015.

quarter of fiscal year 2015.¹² We determined the number of applications approved that used FDA's standard process and the number approved that used one or more of FDA's four expedited programs.¹³ We also analyzed these data to determine the type of drugs FDA approved, such as the product category.

To examine the extent to which FDA's data on tracked safety issues and postmarket studies allowed the agency to meet its reporting and oversight responsibilities, we requested data from FDA on tracked safety issues and postmarket studies and then interviewed FDA officials tasked with compiling those data.¹⁴ We also reviewed the results of internal evaluations conducted by CDER regarding the quality of the data on tracked safety issues and postmarket studies in the agency's internal database.¹⁵ In addition, we interviewed FDA officials concerning these

¹²Efficacy supplements to NDAs and BLAs are applications to make certain changes (e.g., adding a new indication for use) to an approved marketing application. FDA's Center for Biologics Evaluation and Research also reviews certain BLAs for biologics such as blood products, vaccines, and allergenic products. We did not review BLAs reviewed by the Center for Biologics Evaluation and Research; our review included NDAs, BLAs, and efficacy supplements reviewed by CDER.

¹³The data we analyzed may understate the number of approved applications that used the fast track designation prior to November 2013, because, according to FDA officials, reviewers were not required to record the fast track designation in the FDA database at that time. As a result, although FDA had conducted some manual data checks to update the database, some applications approved from October 2006 through November 2013, that we analyzed may have used the fast track designation but were not flagged as such in the data FDA provided and therefore would not be counted in our analysis. FDA required reviewers to enter whether a drug application used the fast track designation beginning on November 29, 2013.

¹⁴Tracked safety issues are potential safety issues with marketed drugs that FDA has determined are significant and are tracked in one of its internal databases. We received and reviewed FDA data on tracked safety issues related to drug applications approved by CDER for the same fiscal year 2007 through the first quarter of fiscal year 2015 period. For postmarket studies, we reviewed data FDA had previously compiled for the HHS Office of Inspector General on postmarketing requirements that were related to applications approved by CDER during fiscal years 2008 through 2014. We used these data and discussions with FDA on shortcomings in these data, to inform our evaluation of the extent to which FDA's data were sufficient for FDA to perform its postmarket reporting and oversight responsibilities.

¹⁵These evaluations were conducted by CDER staff and presented to senior leadership starting in February 2013. We reviewed 5 slide presentations summarizing the results of these evaluations, the latest of which was dated March 2015. According to CDER officials, these slide presentations presented the results of internal evaluations conducted by CDER staff; they do not represent formal FDA findings or conclusions.

internal evaluations and their use of data on tracked safety issues and postmarket studies. We assessed FDA's performance against federal internal control standards.¹⁶

For all three objectives, we reviewed relevant laws and regulations and FDA policy and guidance documents. For our first two objectives, we assessed the reliability of the FDA data by, for example, conducting internal data checks and comparing data FDA provided to us with the agency's publicly available data on drugs approved in a calendar year. We determined that these data were sufficiently reliable for the purposes of this report.

We conducted this performance audit from February 2015 to December 2015 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 four expedited programs—accelerated approval, breakthrough therapy designation, fast track designation, and priority review—are intended to facilitate and expedite development and review of new drugs to address unmet medical needs in the treatment of a serious condition.¹⁷

¹⁶See GAO, *Standards for Internal Control in the Federal Government*, [GAO/AIMD-00-21.3.1](#) (Washington, D.C.: Nov. 1, 1999). Internal control is synonymous with management control and comprises the plans, methods, and procedures used to meet missions, goals, and objectives.

¹⁷In its guidance on expedited programs, FDA defines unmet medical needs as conditions whose treatment or diagnosis are not addressed adequately by available treatments. FDA considers drugs to address an unmet medical need when there are no other available treatments, or when the drug improves upon available treatments. See Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*, (Silver Spring, Md.: May 2014). Drugs may also be reviewed under an expedited program in certain circumstances, such as if a sponsor submits its drug application with a priority review voucher. Priority review vouchers are incentives that are awarded by FDA, for example, after a sponsor develops and receives approval for a drug to treat a rare pediatric disease. The voucher entitles the sponsor to receive priority review for a future drug application of its choosing. As of September 24, 2015, FDA had issued 7 priority review vouchers and had not approved a drug application from a sponsor redeeming a voucher as of December 31, 2014.

According to FDA, these programs are intended to help ensure that drugs for serious conditions are approved and available to patients as soon as it can be concluded that the benefits of the drugs justify their risks. Depending on the specific expedited program, sponsors of new drugs may receive a variety of benefits, such as additional opportunities to meet with and obtain advice from FDA officials during drug development; a rolling review—that is, when FDA reviews portions of the application as they come in instead of waiting for the complete application; the ability to use certain surrogate endpoints or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit; or a shorter goal for review time for the drug application.¹⁸ According to FDA, its expedited programs have the potential to shorten the amount of time necessary for a drug to get to market and to reduce development costs for drug sponsors.¹⁹

There are two different ways that drug applications are selected for review using an expedited program. For breakthrough therapy designation and fast track designation, the sponsor requests and then FDA determines whether to grant or to deny the request, generally during the drug development process before the sponsor submits the application for approval to market the drug.²⁰ For accelerated approval and priority

¹⁸For accelerated approval, a surrogate endpoint is a laboratory measure or physical sign that is reasonably likely to predict clinical benefit, but is not itself a measure of clinical benefit. For example, tumor shrinkage in certain cancer types has been considered reasonably likely to predict an improvement in overall survival. Similarly, for this expedited program, an intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity or mortality and is considered reasonably likely to predict the drug's effect on irreversible morbidity or mortality or other clinical benefit. A clinical endpoint is a direct measure of how a patient feels, functions, or survives.

¹⁹In addition, studies have shown that total development time (i.e., years between initial FDA approval to begin human testing and approval to market the drug) is shorter for drugs approved through an expedited program. For example, a study that examined development times for novel new drugs approved in 2008, and compared expedited programs (fast track designation, accelerated approval, and priority review) to standard review, reported that total development time was shortened by over 2 years, from a median of 7.5 years to a median of 5.1 years. See T. J. Moore and C. D. Furberg, "Development Times, Clinical Testing, Postmarket Follow-up, and Safety Risks for the New Drugs Approved by the U.S. Food and Drug Administration: The Class of 2008," *Journal of the American Medical Association Internal Medicine*, vol. 174, no. 1 (2014).

²⁰FDA can rescind breakthrough therapy designation or fast track designation if a drug no longer meets the qualifying criteria; for example, if another drug is subsequently approved and the drug application under review no longer addresses an unmet medical need. Additionally, the drug sponsor can also withdraw its request for review using an expedited program.

review, sponsors do not submit formal requests. Instead, discussions between drug sponsors and FDA of the appropriateness of accelerated approval generally begin during the drug development process. For priority review designation, FDA assesses each new drug application when it is submitted to determine if it should undergo priority review. Additionally, drug applications can use multiple expedited programs. For example, in December 2014, FDA granted accelerated approval for Lynparza, a drug to treat advanced ovarian cancer—and this drug application also received priority review. See table 1 for a summary of FDA's expedited programs.

Table 1: Summary of the Food and Drug Administration's (FDA) Expedited Programs for Drugs

Expedited program	Qualifying criteria	Description
Accelerated approval	<ul style="list-style-type: none"> Treats a serious condition and drug sponsor demonstrates that a drug generally provides a meaningful advantage over available therapies, and Demonstrates an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug's clinical benefit.^a 	<ul style="list-style-type: none"> Determined as part of the review of the marketing application; sponsors do not submit formal requests for review using this expedited program, but FDA encourages sponsors to communicate regarding a drug's potential for accelerated approval early in drug development. Requires postmarket confirmatory studies to verify and describe anticipated effect on irreversible morbidity or mortality or other clinical benefit. FDA may withdraw approval of the drug or indication approved under accelerated program if the confirmatory studies fail to verify the clinical benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug.
Breakthrough therapy designation	<ul style="list-style-type: none"> Intended to treat a serious condition, and drug sponsor demonstrates that a drug may provide substantial improvement compared with other available treatments based on preliminary clinical evidence. 	<ul style="list-style-type: none"> Requested by the sponsor, generally during the drug's development and testing before the sponsor submits an application for approval for marketing. Features intensive guidance from FDA on efficient drug development, involvement of senior FDA officials, and a rolling review of application materials. FDA can rescind breakthrough therapy designation if drug no longer meets the qualifying criteria.
Fast track designation	<ul style="list-style-type: none"> Intended to treat a serious condition, and drug sponsor provides clinical or nonclinical data that demonstrates a drug's potential to address unmet need, or Drug designated as a qualified infectious disease product.^b 	<ul style="list-style-type: none"> Requested by the sponsor, generally during the drug's development and testing before the sponsor submits an application for approval for marketing. Features increased communication with and guidance from FDA officials and may include a rolling review of application materials. FDA can rescind fast track designation if drug no longer meets the qualifying criteria.

Expedited program	Qualifying criteria	Description
Priority review	<ul style="list-style-type: none"> • Drug treats a serious condition, and, if approved, would provide a significant improvement in safety or effectiveness;^c or • Supplemental application for a drug proposes a labeling change based on certain pediatric studies; or • Drug designated as a qualified infectious disease product; or • Drug application submitted with a priority review voucher. 	<ul style="list-style-type: none"> • Determined by FDA when the sponsor submits its drug application for approval for marketing; that is, FDA considers all applications for priority review and it does not require the sponsor to request it. • Reduces goal for taking action on a drug application from 10 months to 6 months.

Source: GAO summary of FDA information. | GAO-16-192

^aFor accelerated approval, a surrogate endpoint is a laboratory measure or physical sign that is reasonably likely to predict clinical benefit, but is not itself a measure of clinical benefit. For example, tumor shrinkage in certain cancer types has been considered reasonably likely to predict an improvement in overall survival. Similarly, for this expedited program, an intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on irreversible morbidity or mortality and is considered reasonably likely to predict the drug's effect on irreversible morbidity or mortality or other clinical benefit. A clinical endpoint is a direct measure of how a patient feels, functions, or survives.

^bA drug may be designated as a qualified infectious disease product if it is an antibacterial or antifungal drug intended to treat serious or life-threatening infections.

^cAccording to FDA, prior to June 25, 2013, drug applications could qualify for priority review even if the drug product was not intended to treat a serious condition.

FDA has acknowledged that expediting drug application approvals can pose risks for patients. For example, for accelerated approval, FDA guidance states that there is a risk that patients may be exposed to a drug that ultimately will not be shown to provide an actual clinical benefit.²¹ FDA's guidance also states that with fewer, smaller, or shorter clinical trials, there may be less information about rare or delayed adverse events. FDA has stated, however, that its expedited programs do not change the standard of evidence required for approval and that some additional risk may be acceptable because patients and physicians are

²¹Department of Health and Human Services, Food and Drug Administration, *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*, (Silver Spring, Md.: May 2014). Under accelerated approval, a drug application may be approved based on a surrogate or intermediate clinical endpoint with a study to verify the clinical benefit required after the drug is marketed. According to FDA officials, although there is a risk that a drug granted accelerated approval ultimately will not be shown to provide actual clinical benefit, most drugs granted accelerated approval successfully demonstrate clinical benefit.

generally willing to accept greater risk when treating life-threatening and severely debilitating diseases.²²

After FDA approves a drug for marketing, the agency continues to monitor the drug's safety and is required by law to publicly report on certain aspects of its postmarket safety efforts. For example, FDA tracks information about certain potential safety issues, such as serious adverse events and medication errors, in its internal database, the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS).²³ DARRTS is used, among other things, to generate a work plan and assign responsibilities for managing these tracked safety issues, as well as to provide updates on their status. Only those potential safety issues that FDA determines are significant—that is, have the potential to result in FDA taking one or more actions, such as requiring labeling changes—are tracked in DARRTS. FDA is required to publish a quarterly report listing certain potential safety issues that it has identified using its adverse event reporting system; FDA identifies those potential safety issues from among the tracked safety issues in DARRTS.²⁴

Another important aspect of FDA's postmarket safety oversight is monitoring the progress of postmarket studies—conducted after a drug has been approved—that FDA can request or require. Under certain circumstances, FDA can require sponsors to conduct a postmarket study as a condition of approval, such as for drugs granted accelerated

²²To obtain approval to market a drug, a sponsor must demonstrate that the drug is safe and provide evidence, based on adequate and well-controlled trials, that the drug is effective for its intended purpose. 21 U.S.C. § 355(d), 21 C.F.R. § 314.126 (2014).

²³FDA began tracking safety issues in DARRTS in January 2007, in response to a recommendation from our 2006 report, [GAO-06-402](#), and following a report from the Institute of Medicine, *The Future of Drug Safety*. According to FDA, almost 1,000 tracked safety issues were entered into DARRTS from January 2007 to March 2012.

²⁴21 U.S.C. § 355(k)(5)(A). Specifically, FDA is required by law to publish a quarterly report of any new safety information or potential signal of a serious risk identified through its adverse event reporting system within the last quarter. As a matter of process, CDER identifies those safety signals that meet statutory criteria for quarterly reporting from its tracked safety issues. Tracked safety issues that arise from other sources, such as epidemiologic studies or other published literature, are not included in these quarterly reports.

approval.²⁵ The results of postmarket studies provide further information about a drug's safety, efficacy, or optimal use that FDA can use to take one or more actions, such as approving a drug for new uses. Under the accelerated approval program, if sponsors do not conduct the required postmarket study, called a confirmatory trial, with due diligence, or the results of the trial do not confirm the drug's clinical benefit, FDA has the authority to begin procedures for withdrawing the drug's approval for marketing. For example, in 2012, FDA withdrew approval for the NDA for the cancer drug Iressa after the results of its confirmatory trial failed to show an improvement in survival for patients who took it compared with patients who received a placebo. FDA tracks information about postmarket studies, such as their status and projected completion date, in DARRTS.²⁶ FDA is required to publish an annual report in the Federal Register on the status of certain postmarket studies.²⁷ In its past reports, FDA has summarized the number of postmarket studies and the extent to which they were proceeding according to established time frames for completion.

Although FDA is responsible for overseeing postmarket studies and ensuring they are completed in a timely manner, we and others have

²⁵In addition to studies required as a condition of accelerated approval, FDA can also require sponsors to conduct postmarketing studies (1) to assess a known serious risk, assess signals of serious risk, or identify an unexpected serious risk related to the use of a drug when available data indicate the potential for a serious risk; (2) to study certain drugs for pediatric populations, when these drugs are not adequately labeled for use in pediatric populations; and (3) to demonstrate safety and efficacy in humans for a drug approved on the basis of animal efficacy data because human trials were not ethical or feasible. FDA may also request a study known as a postmarketing commitment. A postmarketing commitment is a study that sponsor agrees to, but is not required to conduct after drug approval.

²⁶The status of a postmarket study is determined by FDA based on information from the sponsor about its progress, and is generally determined based on the original schedule. FDA categorizes postmarket studies as open or closed. Open postmarket studies are classified by FDA as pending (not started but not past the date the sponsor projected the study would start); ongoing (proceeding according to or ahead of the original schedule); delayed (proceeding but behind the sponsor's original schedule); terminated (ended before completion, but the sponsor has yet to submit a final report to FDA); or submitted (ended and the sponsor has submitted a final report FDA). Closed postmarket studies are classified by FDA as fulfilled (FDA has determined that the sponsor has met the terms of the commitment or requirement) or released (the sponsor was no longer obligated to conduct the study because it was considered no longer feasible, because it would no longer provide useful information, or because the product was withdrawn).

²⁷21 U.S.C. § 356b(c).

found that, in the past, FDA has not adequately done so. HHS's Office of Inspector General concluded in a 2006 report that FDA could not readily identify whether or how timely postmarket study commitments were progressing toward completion.²⁸ In 2009, we found that FDA had not been routinely monitoring the status of postmarket studies, primarily because oversight of these studies was not considered a priority.²⁹ Both reports note that FDA's inadequate oversight was due, in part, to staff not meeting timeliness goals for the review of submissions from sponsors, such as annual status reports that contain information on the progress of postmarket studies and final reports that include results of completed studies. In 2008, FDA hired a contractor to help meet requirements under the Food and Drug Administration Amendments Act of 2007 (FDAAA) that FDA annually review and report on the "backlog" of postmarket studies, which FDA defined as studies that were open (i.e., not fulfilled or released) as of the date of enactment of FDAAA (September 27, 2007).³⁰ The contractor found that this backlog contained more than 500 postmarket studies where a final report had been submitted that FDA had not yet reviewed, including reports for confirmatory trials that were required for drugs granted accelerated approval.

²⁸This report contained recommendations, including that FDA improve its information system for monitoring postmarketing studies so that it provides timely, accurate, and useful information, and that FDA ensure that postmarketing studies are being monitored. FDA agreed with these recommendations. See Department of Health and Human Services, Office of Inspector General, *FDA's Monitoring of Postmarketing Study Commitments*, OEI-01-04-00390 (Washington, D.C.; June 2006). HHS's Office of Inspector General is currently conducting a study that examines, among other things, how FDA monitors postmarketing requirements.

²⁹See GAO, *New Drug Approval: FDA Needs to Enhance Its Oversight of Drugs Approved on the Basis of Surrogate Endpoints*, [GAO-09-866](#) (Washington, D.C.: Sept. 23, 2009).

³⁰Pub. L. No. 110-85, § 921, 121 Stat. 823, 962 (2007) (adding 21 U.S.C. § 355(k)(5)(C)). According to FDA, the contractor found 63 percent of studies in the backlog were initially labeled as pending, whereas at the end of the contractor's review, 14 percent were labeled as pending.

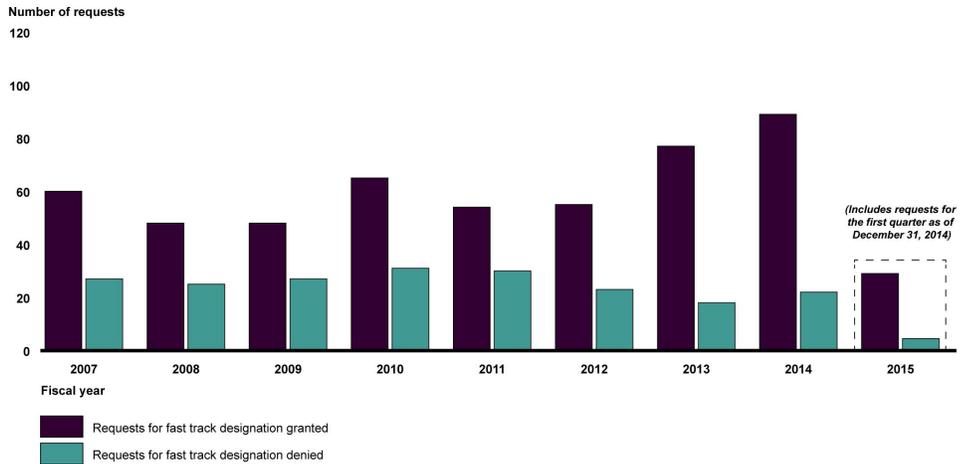
FDA Granted More than Half of Requests for Fast Track Designation and Denied Most Requests for Breakthrough Therapy Designation

FDA Granted Two-Thirds of Requests for Fast Track Designation and Denied Most Requests for Breakthrough Therapy Designation

Of the 772 requests for fast track designation FDA received from October 1, 2006, through December 31, 2014, FDA granted about two-thirds (or 525) of them. By receiving fast track designation, sponsors may have increased communication with and guidance from FDA officials and may have a rolling review of their drug application. FDA denied about one-fourth (or 207) of the requests for fast track designation; according to FDA officials, requests are generally denied because the drug application does not meet the criteria for fast track designation. For example, requests for fast track designation in which the drug is not intended to treat a serious medical condition will be denied. The 40 remaining requests were either withdrawn by the sponsor or categorized as other by FDA.³¹ Since fiscal year 2011, the number of requests FDA has granted fast track designation has increased, from 54 requests granted in fiscal year 2011, to 89 granted in fiscal year 2014. (See fig. 1.)

³¹According to FDA, requests for fast track designation with a status of other include cases where the drug application is inactivated, terminated, or cancelled before FDA made a decision to grant or deny the sponsor's request or FDA's decision on the request was still pending at the time FDA extracted the data for our review.

Figure 1: Requests the Food and Drug Administration (FDA) Granted and Denied for Fast Track Designation, October 2006 through December 2014

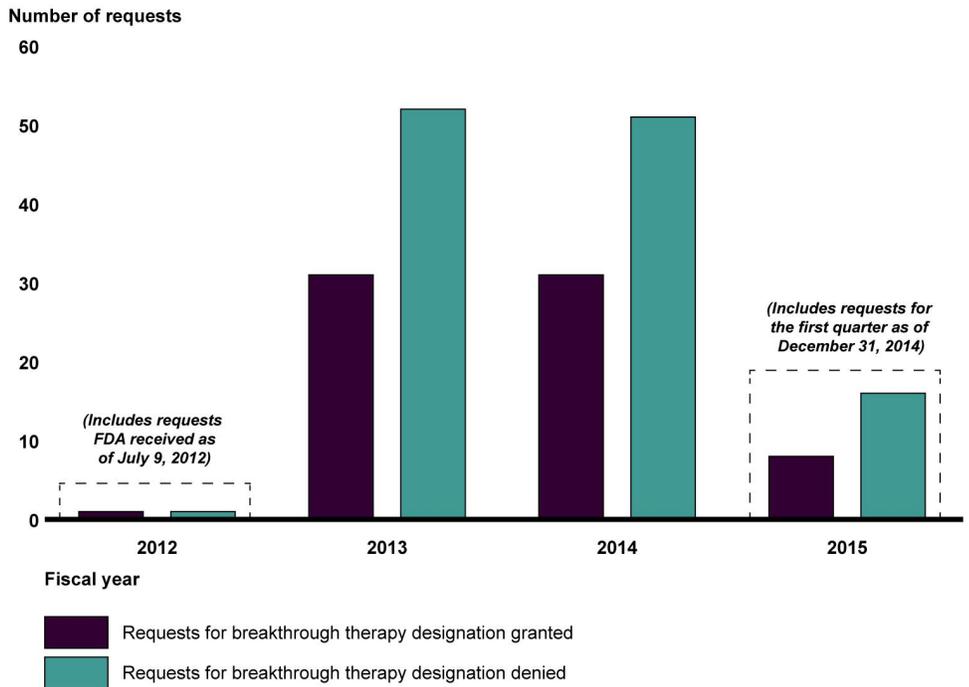


Source: GAO analysis of FDA data. | GAO-16-192

Notes: In addition to requests granted and denied during the period, 33 requests for fast track designation were withdrawn by the sponsor and 7 were classified by FDA as other. According to FDA, the category of other includes cases where the drug application was inactivated, terminated, or cancelled before FDA made a decision (grant or deny) or if the request is still pending.

In contrast to granting most of the requests for fast track designation, FDA denied more than half (or 120) of the 225 requests for breakthrough therapy designation that the agency received since that expedited program was established in July 2012 through the end of December 2014. According to FDA officials, most requests for this designation are denied because of poor study design associated with the request. FDA granted 71 requests for breakthrough therapy designation since the program was established, including 31 requests granted in each of fiscal years 2013 and 2014. (See fig. 2.) According to FDA data, 34 requests for breakthrough therapy designation were withdrawn by the sponsor during the period.

Figure 2: Requests the Food and Drug Administration (FDA) Granted and Denied for Breakthrough Therapy Designation, July 9, 2012, through December 31, 2014



Source: GAO analysis of FDA data. | GAO-16-192

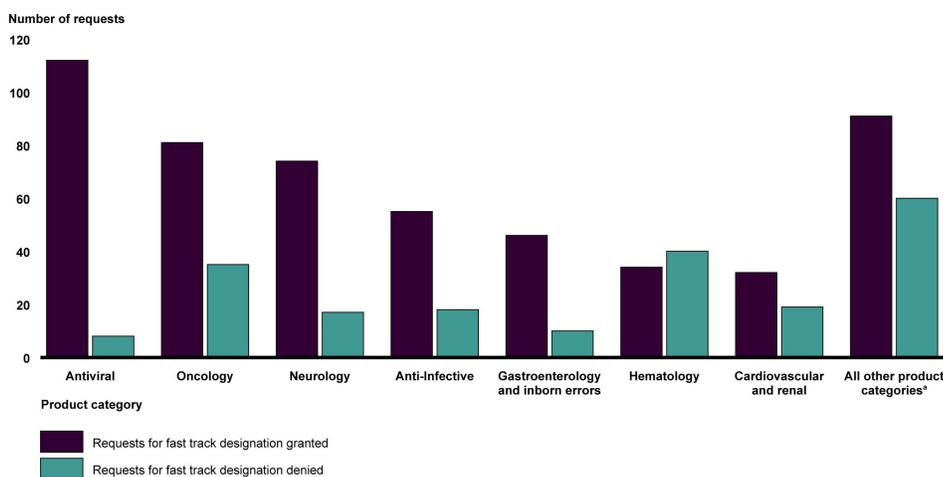
Notes: The breakthrough therapy designation program was established on July 9, 2012. In addition to requests granted and denied, from July 9, 2012, through December 31, 2014, 34 requests were withdrawn by the sponsor.

Antiviral and Oncology Drugs Were the Most Common Product Categories among Applications Granted Fast Track and Breakthrough Therapy Designation

Of the 525 requests for fast track designation that FDA granted from fiscal year 2007 through the first quarter of fiscal year 2015, the most common product category (with 112 requests granted) was for antiviral drugs. For example, Isentress—an antiviral drug to treat human immunodeficiency virus that was approved by FDA in 2007—used fast track designation. This product category was followed by oncology (81 requests granted), neurology (74 requests granted), anti-infectives (55 requests granted), gastroenterology and inborn errors (46 request granted), hematology (34 requests granted), and cardiovascular and renal (32 requests granted). The remaining requests that FDA granted for fast track designation (91

requests) were for drugs in other product categories.³² (See fig. 3.) Appendix I has more information on requests for fast track designation that FDA granted, by product category.

Figure 3: Requests for Fast Track Designation That the Food and Drug Administration (FDA) Granted and Denied, by Product Category, October 2006 through December 2014



Source: GAO analysis of FDA data. | GAO-16-192

Notes: In addition to requests granted and denied during the period, 33 requests for fast track designation were withdrawn by the sponsor and 7 requests were classified by FDA as other. According to FDA, the category of other includes cases where the drug application was inactivated, terminated, or cancelled before FDA made a decision (grant or deny) or if the request is still pending.

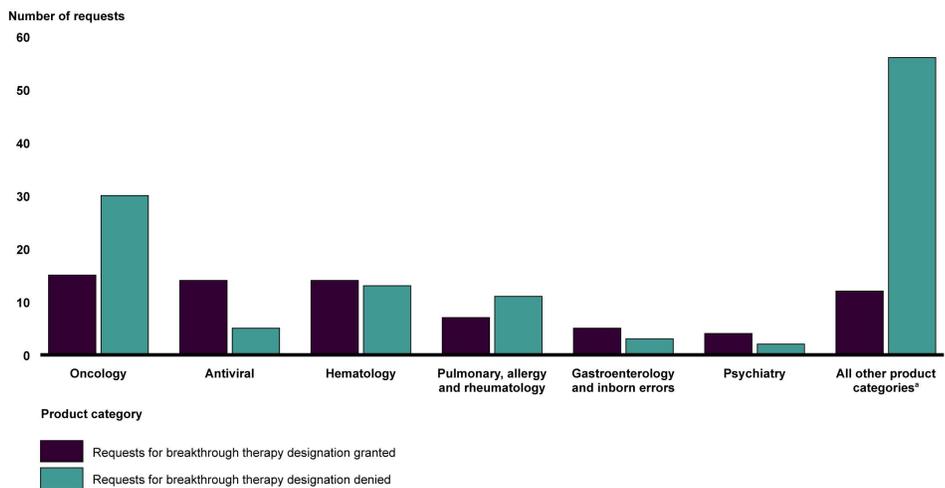
^aAll other product categories includes the following: anesthesia, analgesia, and addiction; bone, reproductive, and urologic; dermatology and dental; medical imaging; metabolism and endocrinology; psychiatry; pulmonary, allergy, and rheumatology; and transplant and ophthalmology. Each of these product categories had fewer than 5 percent of the total fast track designations granted.

The most common product categories among the 71 requests for which FDA granted breakthrough therapy designation from July 9, 2012, through December 31, 2014, were oncology (15 requests granted), antiviral (14 requests granted), and hematology (14 requests granted).

³²The other product categories for which fast track designation was granted—each of which had fewer than 5 percent of the total fast track designations granted—were anesthesia, analgesia, and addiction (23 requests granted); transplant and ophthalmology (19 requests granted); pulmonary, allergy, and rheumatology (17 requests granted); psychiatry (16 requests granted); medical imaging (6 requests granted); bone, reproductive, and urologic (5 requests granted); dermatology and dental (4 requests granted); and metabolism and endocrinology (1 request granted).

For example, FDA granted breakthrough therapy designation for the oncology drug Keytruda (a drug to treat patients with advanced melanoma who are no longer responding to other drugs) because, according to FDA, the sponsor demonstrated through preliminary clinical evidence that the drug may offer a substantial improvement over other therapies. The rest of the requests for breakthrough therapy designation FDA granted were for drugs in the FDA product categories of pulmonology, allergy, and rheumatology (7 requests granted); gastroenterology and inborn errors (5 requests granted); psychiatry (4 requests granted), and other (12 requests granted).³³ (See fig. 4.) Appendix II has more information on requests for breakthrough designation that FDA granted, by product category.

Figure 4: Requests for Breakthrough Therapy Designation That the Food and Drug Administration (FDA) Granted and Denied, by Product Category, July 9, 2012, through December 31, 2014



Source: GAO analysis of FDA data. | GAO-16-192

Notes: The breakthrough therapy designation program was established on July 9, 2012. In addition to requests granted and denied, from July 9, 2012, through December 31, 2014, 34 requests were withdrawn by the sponsor.

³³The other product categories for which breakthrough therapy designation was granted—each of which had fewer than 5 percent of the total breakthrough therapy designations granted—were neurology (3 requests granted); anesthesia, analgesia, and addiction (2 requests granted); anti-infectives (2 requests granted); dermatology and dental (2 requests granted); transplant and ophthalmology (2 requests granted); and cardiovascular and renal (1 request granted).

^aAll other product categories includes the following: anesthesia, analgesia, and addiction; anti-infectives; cardiovascular and renal; dermatology and dental; neurology; and transplant and ophthalmology. Each of these product categories had fewer than 5 percent of the total breakthrough therapy designations granted.

One in Four Drug Applications Approved by FDA Used at Least One Expedited Program, and the Most Frequent Category Was Oncology Drugs

About a quarter of the 1,717 drug applications that FDA approved from October 1, 2006, through December 31, 2014, used at least one expedited program.³⁴ Drug applications may use multiple expedited programs, although most used one program. Of 444 approved drug applications that used one or more expedited programs, 344 (77 percent) used one expedited program, 78 used 2 programs, 20 used 3 programs, and 2 used all four programs.³⁵ (See fig. 5.) Priority review was the most used program, with 408 of the 444 drug applications (92 percent) receiving priority review. (See fig. 6.) Average FDA review time for marketing applications for drugs that used at least one expedited program was less than for drugs that did not. FDA review time was an average of 8.6 months for marketing applications for drugs that used at least one expedited program compared with 12.1 months for marketing applications for drugs that did not.³⁶

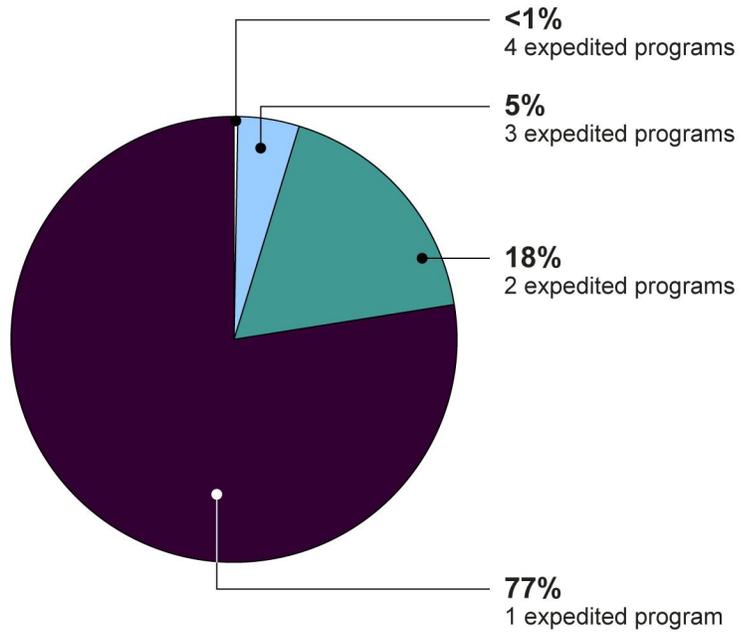
³⁴The 1,717 drug applications included in our review were NDAs, BLAs, and efficacy supplements approved by CDER.

³⁵The new cancer drugs ibrutinib and nivolumab used all four expedited programs. Ibrutinib was approved in November 2013 for a rare form of blood cancer and works by blocking the action of an enzyme that allows cancer cells to grow and divide. Nivolumab was approved in December 2014 to treat skin cancer and works by helping the body's immune system to attack tumors.

³⁶This difference is statistically significant. Results may primarily reflect the effect of priority review, which shortens FDA's goal time for taking action on a marketing application, because most approved applications that used one or more expedited programs received priority review.

Figure 5: Drug Applications Approved by the Food and Drug Administration (FDA) That Used at Least One Expedited Program, Categorized by Number of Expedited Programs, October 2006 through December 2014

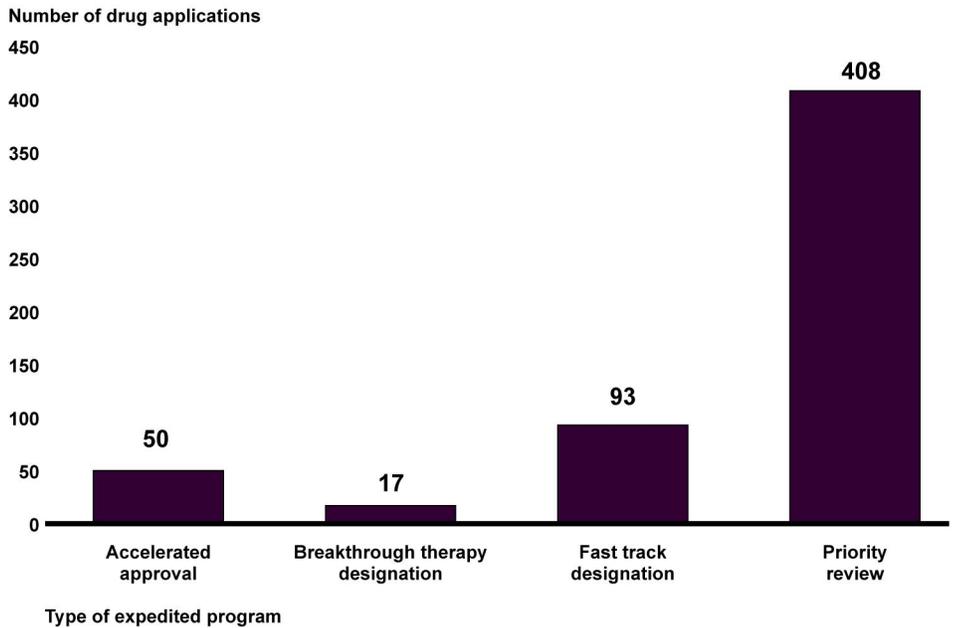
Total=444



Source: GAO analysis of FDA data. | GAO-16-192

Note: FDA's Center for Drug Evaluation and Research approved a total of 1,717 new drug applications, biologic license applications, and efficacy supplements during the period, 444 of which used at least one expedited program. Percentages do not add to 100 due to rounding.

Figure 6: Number of Drug Applications Approved by the Food and Drug Administration (FDA) That Used an Expedited Program, October 2006 through December 2014



Source: GAO analysis of FDA data. | GAO-16-192

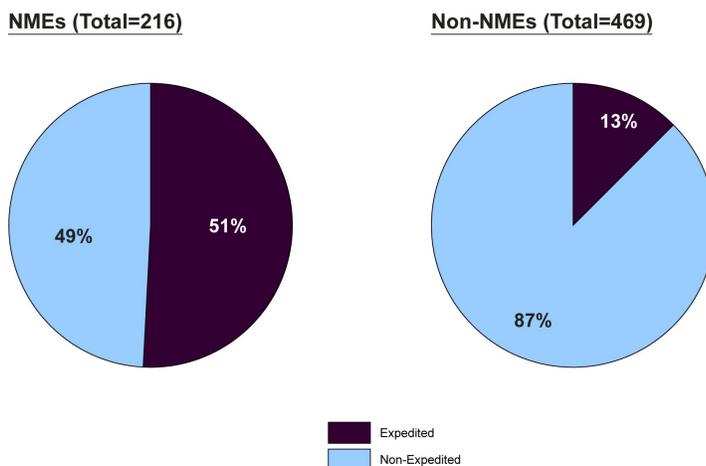
Notes: Includes new drug applications, biologic license applications, and efficacy supplements that were approved by the Center for Drug Evaluation and Research. Does not sum to total number of approved applications that used an expedited program (444) because applications may use more than one expedited program. The number of approved applications that used the fast track designation may be understated, because, according to FDA officials, prior to November 2013, flagging an application as having used the fast track designation in FDA's database was optional. FDA added a prompt for reviewers to enter whether a drug application used the fast track designation on November 29, 2013.

New molecular entities (NME) accounted for 216 (32 percent) of the 685 NDAs that were approved during the time frame of our review.³⁷ NMEs were more likely to have used an expedited program than NDAs that FDA did not designate as NMEs. Of 216 approved applications for NMEs, FDA data identified 110 (51 percent) of them as using at least one expedited

³⁷FDA classifies certain drugs as NMEs for purposes of its review. Many of these products contain active chemical substances that have not been approved by FDA previously. Our analysis of NMEs excludes BLAs and NDA- and BLA-related efficacy supplements because FDA does not classify these applications as NMEs.

program while 59 of the 469 NDAs that were not NMEs (13 percent) used at least one expedited program.³⁸ (See fig. 7.)

Figure 7: Comparison of New Drug Applications (NDA) for New Molecular Entities (NME) and Non-NMEs, October 2006 through December 2014



Source: GAO analysis of FDA data. | GAO-16-192

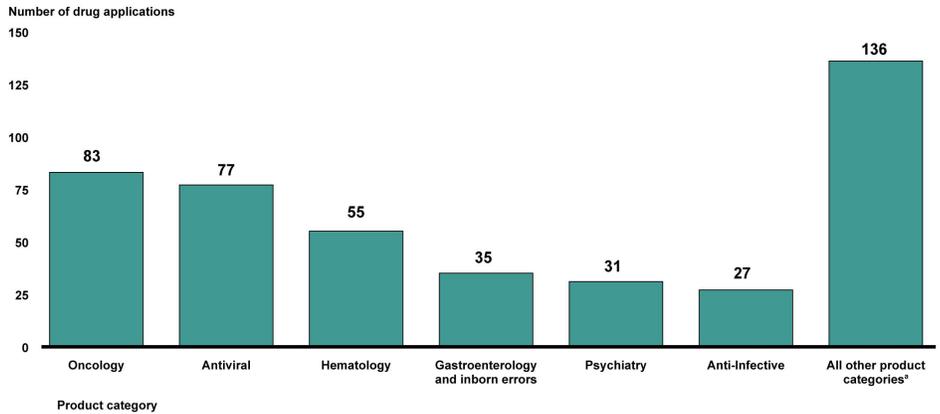
Note: Analysis includes NDAs approved by FDA’s Center for Drug Evaluation and Research. FDA identified approved NDAs as NMEs or non-NMEs in the data we reviewed. FDA does not categorize efficacy supplements or biologic license applications as NMEs.

The most common product category for drug applications approved by FDA from October 1, 2006, through December 31, 2014, that used at least one expedited program was oncology (83 of 444 applications, 19 percent), followed by antiviral (77 applications, 17 percent), and hematology (55 applications, 12 percent). The remaining applications were for drugs in other product categories.³⁹ (See fig. 8.)

³⁸This difference is statistically significant.

³⁹These other product categories were anesthesia, analgesia, and addiction; anti-infectives; bone, reproductive, and urologic; cardiovascular and renal; dermatology and dental; gastroenterology and inborn errors; medical imaging; metabolism and endocrinology; neurology; psychiatry; pulmonary, allergy, and rheumatology; and transplant and ophthalmology.

Figure 8: Number of Drug Applications Approved by the Food and Drug Administration (FDA) That Used at Least One Expedited Program by Product Category, October 2006 through December 2014



Source: GAO analysis of FDA data. | GAO-16-192

^aThe other product categories each represented 5 percent or less of all applications that were approved using an expedited program. These other categories were anesthesia, analgesia, and addiction; bone, reproductive, and urologic; cardiovascular and renal; dermatology and dental; medical imaging; metabolism and endocrinology; neurology; pulmonary, allergy, and rheumatology; and transplant and ophthalmology.

FDA Lacks Reliable Information for Postmarket Safety Reporting and Oversight

FDA lacks reliable, readily accessible data on tracked safety issues and postmarket studies needed to meet certain postmarket safety reporting responsibilities and to conduct systematic oversight. CDER's internal evaluations of data in its DARRTS database revealed problems with the completeness, timeliness, and accuracy of the data. These problems, as well as problems with the way data are recorded that impair their accessibility, have prevented FDA from publishing some required postmarket safety reports in a timely manner, and have restricted its ability to perform systematic oversight. Internal control standards for the federal government specify that information should be recorded in a form and within a time frame that enables staff to carry out their responsibilities and that relevant, reliable, and timely information should be available for external reporting purposes.⁴⁰ Although FDA has taken some steps to address the problems with its data, it lacks comprehensive plans for doing so.

⁴⁰[GAO/AIMD-00-21.3.1.](#)

CDER conducted internal evaluations of its data for tracked safety issues and postmarket studies and found problems with their completeness, timeliness, and accuracy.⁴¹ In addition, our review found that certain information was not readily accessible to FDA staff for analysis.

Data on tracked safety issues were incomplete. CDER's evaluation indicated that the majority of potential safety issues that staff had identified were not being tracked in DARRTS, CDER also identified 144 issues that had not been formally tracked in DARRTS, despite likely meeting CDER's criteria for tracked safety issues.⁴² CDER's evaluation indicated that a possible reason that staff were not entering tracked safety issues into DARRTS was due to the time-consuming nature of data entry and the additional requirements associated with conducting a structured, multidisciplinary review, which staff considered burdensome, especially for more straightforward issues. CDER's evaluation compared the entry of tracked safety issues before and after a change in policy that required additional work and found that staff entered roughly two-thirds fewer new tracked safety issues into DARRTS after the new policy went into effect as compared with the year prior. FDA officials we spoke with acknowledged that staff were not following CDER's policies and procedures for tracking and documenting potential safety issues, but said that given the high workload of its review staff it had prioritized identifying, assessing, and addressing potential safety issues over administrative tracking.

- **Postmarket study data were outdated and contained inaccuracies.** CDER's evaluation showed that information on postmarket study status (e.g., whether the study was proceeding according to schedule or was delayed) was often outdated or otherwise inaccurate, partly due to delays in staff reviewing submissions, such as final study reports, from drug sponsors. For

⁴¹CDER staff performed an evaluation of the tracked safety issue data in DARRTS and presented the results to senior leadership in April 2013, October 2014, and March 2015. CDER's evaluation of postmarket study data in DARRTS was presented to senior leadership in February 2013 and October 2014.

⁴²CDER officials noted that this analysis of safety issues that likely met criteria to be formally tracked had several limitations, including that the process to determine whether a given issue should have been entered into DARRTS as a tracked safety issue was subjective, was performed by staff not involved in the identification or assessment of the safety issues, and was based on limited information about the safety issues.

example, the evaluation found that over half of reviews of sponsors' submissions associated with about 1,400 postmarket studies FDA requested or required from March 2008 to September 2013 were delayed or overdue.⁴³ CDER's evaluation also found inaccuracies in the postmarket study data, such as statuses recorded as pending or ongoing that should have been recorded as delayed, as well as delays in data entry. Over a third (500) of the approximately 1,400 studies had their status updated or corrected during the course of CDER's internal evaluation.⁴⁴ CDER's evaluation indicated that this pattern of results was similar to the findings of the contractor the agency hired in 2008 to review the backlog of postmarket studies.⁴⁵ CDER's internal evaluation of its postmarket study data attributed the data reliability problems to weaknesses in its process that provided numerous opportunities for failures, such as the need to enter data by hand, which could introduce human error, rather than having them automatically populated; lack of automatic linkage between applications and related sponsor submissions, which make them

⁴³Sponsor submissions comprised annual status reports that provide information on the progress of postmarket studies and final reports that include results of completed studies. We defined "delayed" as reviews of these submissions that had been completed later than they should have been based on CDER's goal time frames and "overdue" as reviews that were late with respect to CDER's goal time frames and were still outstanding at the time of CDER's evaluation. The evaluation examined sponsor submissions associated with NDAs and BLAs reviewed by CDER.

⁴⁴FDA officials told us that the 500 updates were as-reported by review staff based on their recollections. They also explained that CDER's analysis could not determine the specific reasons for the status updates—that is, how many of the 500 status updates occurred because (1) a review was not conducted in a timely manner, (2) there was an error in determining or entering the status into DARRTS, or (3) the sponsor had progressed with the study between the time of the last status update and the time of CDER's internal evaluation and the updated data entry.

⁴⁵See Booz Allen Hamilton, *Independent Evaluation of FDA's Prescription Drug User Fee Act – Evaluations and Initiatives; CDER Technical Support and Analysis, Deliverable 2-8: Final Report on the PMR/PMC Backlog Review*, April 10, 2009, accessed November 5, 2015, <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/post-marketingphaseivcommitments/ucm181135.pdf>, and Booz Allen Hamilton, *CDER Analysis, Evaluation and Technical Assistance, Deliverable 6: Final Report on the PMR/PMC Backlog Review*, March 12, 2010, accessed October 29, 2015, <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/post-marketingphaseivcommitments/ucm232880.pdf>. FDA is required to report annually to Congress on the backlog of postmarket studies—which FDA defined as studies that were open (i.e., not fulfilled or released) as of September 27, 2007—and to assign start dates and estimated completion dates for such studies.

harder to locate; and limited oversight of core steps in the process. FDA officials we spoke with also indicated that staffing limitations and competing priorities contributed to problems identified with the postmarket study data.⁴⁶

- **Tracked safety issue and postmarket study data were not readily accessible to staff for analysis.** FDA officials told us that DARRTS cannot be queried to determine characteristics of tracked safety issues, such as the therapeutic area of the drug associated with a safety issue, the population affected, or what regulatory actions, if any, FDA took in response to a tracked safety issue. Officials said that such information is contained in the text of electronic documents and must be manually reviewed. Similarly, FDA officials told us that some information about postmarket studies, such as the date FDA requested or required a study, must be manually collected from the text of letters to sponsors; these letters are not automatically linked to information about the study in DARRTS, which can make them challenging to locate.⁴⁷

FDA's lack of reliable, readily accessible postmarket safety data has prevented the agency from publishing required reports in a timely manner and has restricted its ability to conduct systematic oversight.

- **Lack of complete, timely, and accurate data has resulted in FDA not publishing required reports in a timely manner.** As of October 2015, FDA had not published required quarterly reports on potential safety issues identified through its adverse event reporting system for calendar year 2015; FDA officials said they had delayed the report covering January through March 2015 due to ongoing efforts to

⁴⁶FDA officials we spoke with said that CDER does not have enough review staff because of, among other things, staff attrition and difficulties in recruiting staff with specialized skills. Officials estimated that the Office of New Drugs within CDER was approximately 10 percent under its authorized staffing ceiling. They also said that competing priorities, such as the need to review drug applications within time frames established by Prescription Drug User Fee Act, and communicate with external stakeholders, had forced the agency to prioritize its work. For example, although final study reports are expected to be reviewed within 12 months of receipt, officials said that this is an aspirational goal and dependent on resources and staffing capacity.

⁴⁷Officials told us that while they can estimate the date a study was requested or required using a proxy method, this method relies on data that are not always complete or accurate and still requires manual review to correct discrepancies.

evaluate the data on tracked safety issues.⁴⁸ CDER's internal evaluation found that the number of tracked safety issues included in quarterly reports during the time frame of its review showed a steep decline that did not accurately reflect the agency's actual efforts to identify and evaluate safety issues. In addition, as of October 2015, FDA had not published required annual reports containing data on postmarket studies for fiscal years 2013 and 2014.⁴⁹ FDA officials told us that they had decided to delay publication of the reports primarily due to CDER's internal evaluation of the postmarket study data and subsequent efforts to address the data problems that were identified.⁵⁰

- **Lack of reliable and accessible data restricts FDA's ability to conduct systematic oversight of postmarket safety.** CDER's evaluation of tracked safety issues found that when issues were not centrally tracked in DARRTS, they were generally visible only to staff within the division or office that had identified them, which prevented senior management from using DARRTS to systematically determine whether safety issues were being evaluated and actions were being taken within reasonable time frames. FDA officials subsequently told us that they have other mechanisms for informing management about potential safety issues outside of DARRTS, such as including them in weekly reports that are discussed at senior management team meetings; however, none of these mechanisms is comprehensive of all potential safety issues CDER staff are evaluating. FDA officials also told us that they cannot readily conduct certain analyses, such as how often and what type of actions FDA has taken for drugs by therapeutic area (e.g., oncology or psychiatry drugs). Similarly, problems with FDA's postmarket study data limit FDA's ability to conduct certain analyses. Inability to quickly determine when postmarket studies were established, for example, does not allow

⁴⁸As of October 2015, the most recent quarterly report available on FDA's website was for October through December 2014, which FDA posted on July 28, 2015.

⁴⁹As of October 2015, the most recent annual report in the Federal Register was for fiscal year 2012. See Notice of Availability, Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Requirements and Commitments; Availability, 79 Fed. Reg. 9230 (Feb. 18, 2014).

⁵⁰FDA has also delayed publishing mandated annual reports to Congress on its backlog of postmarket studies (studies that were open (i.e., not fulfilled or released) as of September 27, 2007). FDA submitted reports to Congress covering fiscal years 2012, 2013, and 2014 in November 2015.

agency staff to readily construct cohorts of studies requested or required in a given fiscal year, which would be necessary for FDA to conduct analyses on completion rates over time, or to review information on studies that were requested or required before and after certain legislative or policy changes to examine their effect.

FDA has reported taking steps to address the problems it identified with the postmarket safety data in DARRTS, but the agency does not have comprehensive plans with goals and time frames.

- **FDA intends to address its incomplete data on tracked safety issues by revising and streamlining its processes for reviewing and tracking these issues.** FDA officials said that CDER has formed a workgroup that is considering options to clarify which potential safety issues should be centrally tracked, and how the tracking and review processes could be streamlined. Officials did not provide an estimate for when these processes would be revised. In the meantime, the Office of New Drugs within CDER issued an interim set of guidelines for staff in April 2015 that state that all potential safety issues requiring further evaluation must be entered into DARRTS. The guidelines also instruct staff to retroactively enter tracked safety issues into DARRTS to enhance the completeness of the data.⁵¹ According to FDA officials, these guidelines are an interim measure to provide key information to staff while CDER's processes for reviewing and tracking safety issues are being revised.
- **FDA intends to increase the timeliness and accuracy of its postmarket study data by improving tools for oversight and data collection.** FDA officials said the agency is aiming to facilitate more timely review of sponsor submissions that contain information on postmarket studies by improving internal oversight. In the fall of 2014, FDA implemented new reporting capabilities that provide information to the review divisions within CDER on a monthly basis about all open postmarket studies those divisions oversee, such as annual status reports and final reports received from sponsors and what the goal dates are for their review. Officials said they have also begun meeting with the Office of Business Informatics within CDER to discuss improvements that could be made in FDA's new information

⁵¹ Officials said that as of August 2015, 102 tracked safety issues had been retroactively entered into DARRTS. CDER aims to complete retroactive entry of tracked safety issues by March 30, 2016.

technology platform, such as automated collection of certain types of data. FDA officials told us that the new platform will include the date FDA requested or required a postmarket study in a form that can be queried.⁵²

- **FDA lacks comprehensive plans to address the problems with its tracked safety issue and postmarket study data.** FDA officials told us that, while the agency has multiple efforts under way to improve its tracked safety issue and postmarket study data, it has not developed plans that comprehensively outline these efforts, establish related goals, and provide time frames for their completion. Additionally, FDA officials said they do not have plans to analyze tracked safety issue and postmarket study data to inform the agency's oversight of its expedited programs, such as determining if drugs that used an expedited program were subsequently associated with tracked safety issues at rates or of types that differed from drugs that used FDA's standard process. FDA officials said that they do not subject applications that used an expedited program to greater postmarket safety monitoring and they do not have plans to do so because, to obtain approval for marketing, these applications are required to meet the same standard of evidence for safety and effectiveness as are applications that used FDA's standard process.⁵³ However, some of the expedited programs specifically permit the use of fewer, shorter, or smaller clinical trials during development, and FDA's lack of analysis means that the agency lacks comprehensive information on whether drugs that were developed under these programs pose additional safety risks to patients once they are available on the market.

⁵²FDA is in the process of implementing its new informatics platform, Panorama, and plans to move away from using DARRTS once it is fully in place. Officials told us that they do not expect Panorama to take on postmarket safety functions within the next 3 years and did not provide an estimate of when this would occur. In the meantime, officials said that the Office of Business Informatics has added the capability in DARRTS to record the date studies were requested or required; this information will be entered for all new postmarket studies as of October 1, 2015.

⁵³Although FDA has noted that greater risk may be acceptable for drugs that treat life-threatening and severely debilitating diseases, FDA officials also told us that they consider whether or not a drug used an expedited program to be a poor indicator for the need for enhanced postmarket monitoring. For example, officials said it is possible that a postmarket study related to an expedited application might examine a safety issue that affects a small number of patients, whereas a study not related to an expedited application might examine a safety issue with the potential to affect a large number of patients.

Conclusions

Complete, accurate, and timely postmarket safety data, such as information on tracked safety issues and the progress of postmarket studies, are essential for FDA to meet its responsibility to monitor the safety of marketed drugs. FDA's monitoring efforts once drugs reach the market are particularly important for those drugs that have used certain expedited programs to reduce the development time before approval, where there may be greater potential for previously unrecognized safety issues to appear once a drug is more widely used. FDA has supported efforts to shorten development and streamline the agency's review of drug applications through expedited pathways. However, we found problems with the agency's efforts to oversee and track potential safety issues and postmarket studies once those drugs are on the market. While internal control standards for the federal government specify that information should be recorded in a form and within a time frame that enables staff to carry out their responsibilities and that relevant, reliable, and timely information should be available for external reporting purposes, FDA's data on postmarket safety issues and studies were found to be incomplete, outdated, to contain inaccuracies, and to be stored in a manner that made routine, systematic analysis difficult.

To effectively track potential safety issues and the agency's response to them, and to track and ensure postmarket studies are being conducted on schedule, it is important that FDA have ready access to complete, timely, and accurate information. This information also provides the basis for FDA's required reports, which are important for informing policymakers and the public about emerging safety issues and the extent to which drug sponsors are fulfilling their obligations to conduct studies on the safety, efficacy, and optimal use of marketed drugs. Reliable and accessible data would also provide FDA with information to conduct analyses to inform oversight of its expedited programs. Although FDA officials have pointed out that all applications have to meet the same statutory standards for approval, and that additional risks posed by applications that used an expedited program may be acceptable given the seriousness of conditions being treated, we believe that reliable data to support additional oversight is important given public concern about the safety implications of streamlined drug development and review. While FDA has begun some efforts to improve its data by issuing guidelines for staff and adding tools for oversight, more concrete plans to correct known problems with the completeness, timeliness, and accuracy of its data, and to improve underlying data systems so that information important for oversight is captured in a useable form, are critical.

Recommendations for Executive Action

To improve the data on tracked safety issues and postmarket studies that are needed for required reporting and for systematic oversight of postmarket drug safety, we recommend that the Secretary of HHS direct the Commissioner of FDA to take the following two actions:

- develop comprehensive plans, with goals and time frames, to help ensure that identified problems with the completeness, timeliness, and accuracy of information in its database on tracked safety issues and postmarket studies are corrected, and
- work with stakeholders within FDA to identify additional improvements that could be made to FDA's current database or future information technology investments to capture information in a form that can be easily and systematically used by staff for oversight purposes.

Agency Comments and Our Evaluation

We provided a draft of this report to HHS for comment. In its written comments, reproduced in appendix III, HHS concurred with our recommendations and stated that conducting rigorous oversight of postmarket safety is a priority. HHS noted that FDA, by improving its data on postmarket studies and tracked safety issues, can more effectively use these data to monitor drugs in the postmarket setting. HHS also provided technical comments that we incorporated, as appropriate.

In addition, HHS commented that drugs using an expedited program must meet the same statutory standards for safety and effectiveness to be approved for the U.S. market as other, non-expedited drugs—a point that is included in our report. HHS noted that drugs using the accelerated approval program are also required to complete postmarket studies for the drug sponsors to verify the anticipated clinical benefits. We believe that this reliance on postapproval studies for verification of the clinical benefits of drugs entering the U.S. market using accelerated approval underscores the importance of improved FDA oversight of postmarket studies. HHS also pointed out the differences between the standards for granting breakthrough therapy designation or fast track designation—that is, the ability for a drug sponsor to use one of these two expedited programs—and FDA approval of the drugs for marketing; these distinctions are also noted in our report.

HHS also commented that FDA-approved drugs that used an expedited program do not necessarily require different postmarket safety monitoring than other drugs, noting that tracked safety issues and postmarket studies are utilized to monitor all drugs after they are approved by FDA,

including drugs using an expedited program. However, as we note in our report, some of the expedited programs specifically permit the use of fewer, shorter, or smaller clinical trials during development, and FDA has noted that additional risks posed by applications that use an expedited program may be acceptable given the seriousness of conditions being treated. FDA's lack of analysis of data on tracked safety issues and postmarket studies related to applications that used an expedited program indicates that the agency lacks comprehensive information on whether drugs that were developed under these programs pose additional safety risks to patients once they are available on the market. We believe that maintaining reliable data that could be used to conduct such analysis is critical, given public concern about the safety implications of streamlined drug development and review.

HHS acknowledged the challenges of FDA's administrative tracking of postmarket safety issues and commented that CDER's internal evaluations, which CDER initiated before we started our review, had helped identify these challenges. HHS further noted that FDA is taking steps to address some of these challenges related to its internal data. HHS also listed other mechanisms FDA uses to monitor postmarket safety issues and the status of its "backlog" of postmarket studies, noting that CDER staff prioritized identifying, evaluating, communicating about, and taking regulatory action to address safety issues over expending limited resources on entering information about safety issues into FDA's tracking system. Nonetheless, given that FDA's internal evaluations found that information on postmarket studies was often outdated or otherwise inaccurate, we continue to believe that complete, accurate, and timely data are necessary for FDA managers to have the information required to conduct systematic oversight and appropriately monitor tracked safety issues and postmarket studies.

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 Secretary of Health and Human Services and other interested parties. In addition, the report will be available at no charge on the GAO website at <http://www.gao.gov>.

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

Sincerely yours,

A handwritten signature in black ink that reads "Marcia Crosse". The signature is written in a cursive style with a long horizontal flourish at the end.

Marcia Crosse,
Director, Health Care

Appendix I: Number of Granted Requests for Fast Track Designation by Product Category, Fiscal Years 2007 through 2015

Number granted fast track designation by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research, by fiscal year

Product category	2007	2008	2009	2010	2011	2012	2013	2014	2015 ^a	2007-2015 ^a	%
Antiviral	13	9	11	23	20	8	13	12	3	112	21.3
Oncology	14	4	7	9	10	9	8	18	2	81	15.4
Neurology	6	11	9	8	8	6	8	14	4	74	14.1
Anti-infective	5	3	2	4	1	4	15	15	6	55	10.5
Gastroenterology and inborn errors	6	2	6	4	6	6	6	6	4	46	8.8
Hematology	3	1	2	4	3	6	5	8	2	34	6.5
Cardiovascular and renal	7	4	5	2	1	4	3	5	1	32	6.1
Anesthesia, analgesia, and addiction	0	4	0	3	2	3	4	7	0	23	4.4
Transplant and ophthalmology	3	2	2	3	1	2	1	0	5	19	3.6
Pulmonary, allergy, and rheumatology	2	4	3	2	2	1	2	0	1	17	3.2
Psychiatry	0	1	1	1	0	5	6	2	0	16	3.1
Medical imaging	0	2	0	1	0	0	2	1	0	6	1.1
Bone, reproductive, and urologic	0	1	0	1	0	0	2	0	1	5	1.0
Dermatology and dental	1	0	0	0	0	1	1	1	0	4	0.8
Metabolism and endocrinology	0	0	0	0	0	0	1	0	0	1	0.2
Total	60	48	48	65	54	55	77	89	29	525	100.0

Source: GAO analysis of FDA data. | GAO-16-192

Notes: FDA product categories generally correspond to the FDA review division.

^aData for fiscal year 2015 include requests through the first quarter (as of December 31, 2014).

Appendix II: Number of Granted Requests for Breakthrough Therapy Designation by Product Category, July 9, 2012, through December 31, 2014

Number granted breakthrough therapy designation by the Food and Drug Administration's (FDA) Center for Drug Evaluation and Research, by fiscal year

Product category	2012 ^a	2013	2014	2015 ^b	2012-2015 ^{a,b}	%
Oncology	0	6	7	2	15	21.1
Antiviral	0	8	5	1	14	19.7
Hematology	0	7	7	0	14	19.7
Pulmonary, allergy, and rheumatology	1	1	3	2	7	9.9
Gastroenterology and inborn errors	0	3	1	1	5	7.0
Psychiatry	0	1	2	1	4	5.6
Neurology	0	3	0	0	3	4.2
Anesthesia, analgesia, and addiction	0	0	2	0	2	2.8
Anti-infective	0	0	2	0	2	2.8
Dermatology and dental	0	1	1	0	2	2.8
Transplant and ophthalmology	0	0	1	1	2	2.8
Cardiovascular and renal	0	1	0	0	1	1.4
Total	1	31	31	8	71	100.0

Source: GAO analysis of FDA data. | GAO-16-192

Notes: Breakthrough therapy designation was established under the Food and Drug Administration Safety and Innovation Act, enacted on July 9, 2012. FDA product categories generally correspond to the FDA review division.

Percentage rows do not sum to 100 due to rounding.

^aData for fiscal year 2012 include requests FDA received as of July 9, 2012.

^bData for fiscal year 2015 include requests through the first quarter (as of December 31, 2014).

Appendix III: 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

DEC 0 1 2015

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

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement" (GAO-16-192).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

A handwritten signature in cursive script that reads "Jim R. Esquea".

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

**DRAFT REPORT GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH
AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY
OFFICE'S DRAFT REPORT ENTITLED: DRUG SAFETY: FDA EXPEDITES
MANY APPLICATIONS BUT DATA FOR POSTAPPROVAL OVERSIGHT NEED
IMPROVEMENT (GAO-16-192)**

The Department appreciates the opportunity to review and comment on GAO's draft report. HHS is committed to robust oversight of drug safety, a critical component of our public health mission for drugs, both pre- and post-approval.

FDA would like to clarify three points. First, to be approved, all drugs must meet the same statutory standards for safety and effectiveness. This is the case whether or not a given drug has been the subject of an expedited development program. Second, approved drugs that were the subject of expedited programs do not necessarily require different postmarket safety monitoring from those approved outside of those programs. Finally, through processes for continuous improvement conducted prior to the initiation of this GAO study, HHS recognized challenges related to administrative tracking of its postmarket safety work, and, consistent with GAO's recommendation, is currently addressing those concerns through ongoing improvement efforts.

Approved drugs that have been the subject of one or more expedited programs must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

FDA's four expedited programs—fast track designation, breakthrough therapy designation, priority review designation, and accelerated approval—are intended to facilitate and expedite development and review of new drugs to address unmet medical needs in the treatment of serious or life-threatening conditions. Each program rests on the basic premise that to be approved for marketing the drug must be found to meet statutory standards for safety and effectiveness. These standards are not altered by any of the expedited programs. For effectiveness, that standard is substantial evidence based on adequate and well-controlled clinical investigations. For safety, the standard is having sufficient information to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling.

FDA's *Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics (May 2014)* describes the policies, procedures, and unique features of the four programs, as well as eligibility criteria for these expedited programs. Fast track and breakthrough therapy programs involve more frequent interactions with FDA or intensive guidance from the agency to facilitate development. The priority review program involves a shorter goal timeframe for review of a marketing application and does not affect development time. The accelerated approval program is characterized by, among other features, approval of a drug that demonstrates an effect on a surrogate endpoint, or an intermediate clinical endpoint, that is reasonably likely to predict clinical benefit. Of note, while FDA has observed that there may be “fewer, smaller, or shorter clinical trials” for drugs granted accelerated approval, the sponsor must still demonstrate by substantial evidence the safety and effectiveness of the drug. Moreover, the accelerated approval pathway also includes postmarketing study requirements for the sponsor to verify the

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anticipated clinical benefit. In the rare cases where clinical benefit is not confirmed post-approval, FDA has the authority to conduct expedited withdrawal of the drug or the indication from the market.

It is also important to recognize that the standards for *designation* under the breakthrough therapy and fast track programs are **not** the same as the FDA standards for *drug approval*. For example, the clinical evidence needed to support breakthrough therapy designation is generally preliminary. In contrast, a more extensive set of data are needed to support approval of a marketing application. Each approval decision must factor in the specific benefits and risks of the proposed drug and its intended use, based on FDA's review of the full data submitted. FDA's approval standards are based on the fundamental statutory requirements, which are therefore not altered by the use of expedited programs.

Oversight of drug safety is a critical component of FDA's public health mission for drugs, both pre- and post-approval. Approved drugs that were the subject of expedited programs do not necessarily require different postmarket safety monitoring than other drugs.

FDA monitors and reviews safety information about all drugs throughout their lifecycles, interacting with sponsors during product development and clinical investigation of the drugs, closely reviewing safety issues during consideration of marketing applications, and, if the drugs are approved, monitoring safety reports after the drugs are marketed. After drug approval, FDA may learn of new, more serious, or more frequent adverse drug reactions from, for example, post-approval voluntary or mandatory reporting of adverse drug reactions during use of the drug; post-approval clinical trials exploring new uses of the drug; or other post-approval studies, including epidemiologic studies or active surveillance evaluations. The FDA's Center for Drug Evaluation and Research (CDER) integrates what it learns from required sponsor reporting and its own evaluations into an overall system of postmarketing surveillance and risk assessment. The Center then uses this information to take appropriate action when the risks identified indicate a need to provide additional safety information to the public, update drug labeling, require postmarketing studies or trials, require additional risk management interventions, or, on rare occasions, withdraw approval of a drug.

Two of the mechanisms that CDER uses to further evaluate a drug after it has been approved are postmarketing requirements (PMRs) and focused tracking of certain postmarketing safety issues (tracked safety issues or TSIs). Very generally, PMRs are studies or clinical trials that gather additional information about the safety, efficacy, or optimal use of an approved drug, and which sponsors are required to conduct by statute or regulation. A PMR can be put in place at the time a drug is approved or any time a new safety issue is identified. TSIs represent those postmarketing safety issues that are considered "significant" according to pre-specified threshold criteria; are entered into

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CDER's tracking system¹; and for which multi-disciplinary teams are formed to evaluate the issue and determine the need for regulatory action. TSIs can be put in place at any time once a product is on the market.

These same tools are utilized for drugs that have been the subject of expedited development and review programs and can take into account what was learned during development and the nature of the population to be treated. For example, for drugs granted accelerated approval, PMRs have been required to verify and describe the anticipated clinical benefit, and also yield supplemental postmarket safety information.

FDA conducts rigorous oversight of postmarket safety issues, despite certain challenges related to administrative tracking of postmarket safety work. Through its own processes for continuous improvement, FDA recognized these challenges prior to initiation of the GAO study and is currently addressing those concerns through ongoing improvement efforts.

Tracked Safety Issues

Well before this GAO study, CDER recognized that our administrative tracking of TSIs needed improvement. CDER determined that the number of TSIs entered into its tracking system was low compared the number of postmarketing safety issues already identified and/or under evaluation by CDER staff. However, the work to identify, evaluate, and address postmarketing safety issues was and is being conducted. This is evidenced by the numerous actions FDA has taken to address postmarketing safety issues. For example, in calendar years 2012-2014, labeling changes related to safety were made to about 45 approved drug products each month through processes initiated by both FDA and sponsors.² Given the high workload of review staff and limited available resources, CDER staff prioritized fully identifying, evaluating, communicating about, and taking appropriate regulatory action to address safety issues, over expending limited resources on entering information about the safety issues into our tracking system. This does not mean that review work undertaken is not being documented; only that it was not documented as formal "tracked safety issues" in CDER's tracking system.

The TSI process is only one of the ways in which information about significant postmarketing safety issues is shared within the Center. CDER also uses complementary mechanisms to track and keep management apprised of postmarketing safety issues. Examples of these mechanisms include:

¹ Currently, TSIs are tracked in CDER's Document Archival, Retrieval and Reporting System (DARRTS).

² See FDA's MedWatch web page, at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/default.htm>

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- Weekly reports to the Office of New Drugs Senior Management Team, which highlight important post market drug safety issues that have been identified;
- Joint safety meetings between the Office of New Drugs and the Office of Surveillance and Epidemiology (OSE);
- The European Medicines Agency-FDA Pharmacovigilance (EMA-FDA PV) Cluster Meetings; and
- Monthly evaluations by the Division of Clinical Review (DCR) in the Office of Generic Drugs to search and assess the FDA Drug Quality Reporting System (DQRS).

Postmarketing Requirements and Commitments

FDA has continually worked to improve its ability to maintain accurate and timely data on the status of PMRs and postmarketing commitments (PMCs). A recent internal evaluation of our data, which began in 2014 and continued into 2015, resulted in updates and corrections to our data, even while GAO was doing its assessment. These activities have resulted in CDER implementing additional oversight mechanisms to ensure the timeliness and accuracy of PMR/PMC data.

Despite the identified challenges with FDA's database on PMRs and PMCs, these data continue to demonstrate that sponsors are conducting their postmarketing studies and trials:

- After completion of the seventh annual review of the "backlog"³ of PMRs and PMCs (as of September 30, 2014), 87% (1,354/1,554) of the PMRs and PMCs in CDER's "backlog" have been closed (i.e., fulfilled or released).
- FDA's most recent annual assessment of the status of PMRs and PMCs overall⁴ found that, as of September 30, 2014, most open PMRs (87% for NDAs and 88% for BLAs) and most open PMCs (68% for NDAs and 77% for BLAs) are progressing on schedule. Thus, at the end of that same fiscal year, only 13% of

³ Section 921 of Title IX of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended section 505(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) by adding a provision requiring the FDA to "on an annual basis, review the entire backlog of postmarketing safety commitments to determine which commitments require revision or should be eliminated, report to the Congress on these determinations, and assign start dates and estimated completion dates for such commitments." The "backlog" consists of all PMRs and PMCs that were open (not yet released or fulfilled) as of the date of enactment of FDAAA. The FDA's seventh annual review of the PMR/PMC "backlog" is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-marketingPhaseIVCommitments/UCM472973.pdf>.

⁴ Under section 506B of the Food, Drug, and Cosmetic Act, the FDA is required to report annually in the Federal Register on the status of postmarketing requirements and commitments required of, or agreed upon by, holders of approved drug and biological products.

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the open NDA PMRs were delayed and only 11% of the open BLA PMRs were delayed.⁵

Ongoing Improvement Efforts

Based on its self-initiated evaluations, HHS has already taken steps to implement new processes and procedures to address the gaps and correct – as indicated – its data on PMRs/PMCs and TSIs. For example, CDER has implemented data entry and tracking procedures and measures to improve available informatics tools to ensure the timeliness and accuracy of its data on the status of PMRs and PMCs. Additionally, CDER has begun to retroactively enter information into its tracking system about TSIs that were previously identified, evaluated and/or acted upon. Furthermore, CDER is actively engaged in activities to increase and/or streamline the capture of specific information into its tracking system, to facilitate additional analyses for oversight of postmarketing studies and safety issues.

HHS Response to GAO Recommendation

Conducting rigorous oversight of postmarketing safety issues is a priority for HHS, and the agency is committed to completing implementation of measures that advance this priority. Therefore, HHS concurs with GAO's recommendation that FDA establish comprehensive plans to improve processes for capture of PMR/PMC and TSI data, and to correct the identified problems with the data, so that these data can be most effectively used to monitor drugs in the postmarketing setting.

⁵ FDA plans to present this information in its forthcoming FY 2014 Federal Register report on the status of postmarketing requirements and commitments.

Appendix IV: GAO Contact and Staff Acknowledgments

GAO Contact

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

Staff Acknowledgments

In addition to the contact named above, Kim Yamane, Assistant Director; Marisa Beatley; Carolyn Fitzgerald; Sandra George; Cathleen Hamann; Gay Hee Lee; Jessica Lin; and Hannah Locke were major contributors to this report.

Appendix V: Accessible Data

Agency Comments

Text of Appendix III Comments from the Department of Health and Human Services

Page 1

Marcia Crosse Director, Health Care

U.S. Government Accountability Office 441 G Street NW

Washington, DC 20548 Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "FDA Expedites Many Applications, But Data for Postapproval Oversight Need Improvement" (GAO-16-192) .

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

Assistant Secretary for Legislation

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FDA would like to clarify three points. First, to be approved, all drugs must meet the same statutory standards for safety and effectiveness. This is the case whether or not a given drug has been the subject of an expedited development program. Second, approved drugs that were the subject of expedited programs do not necessarily require different postmarket safety monitoring from those approved outside of those programs. Finally, through processes for continuous improvement conducted prior to the initiation of this GAO study, HHS recognized challenges related to administrative tracking of its postmarket safety work,

and, consistent with GAO's recommendation, is currently addressing those concerns through ongoing improvement efforts.

Approved drugs that have been the subject of one or more expedited programs must meet the same statutory standards for safety and effectiveness as those granted traditional approval.

FDA's four expedited programs—fast track designation, breakthrough therapy designation, priority review designation, and accelerated approval—are intended to facilitate and expedite development and review of new drugs to address unmet medical needs in the treatment of serious or life-threatening conditions. Each program rests on the basic premise that to be approved for marketing the drug must be found to meet statutory standards for safety and effectiveness. These standards are not altered by any of the expedited programs. For effectiveness, that standard is substantial evidence based on adequate and well-controlled clinical investigations. For safety, the standard is having sufficient information to determine whether the drug is safe for use under conditions prescribed, recommended, or suggested in the proposed labeling.

FDA's Guidance for Industry Expedited Programs for Serious Conditions—Drugs and Biologics (May 2014) describes the policies, procedures, and unique features of the four programs, as well as eligibility criteria for these expedited programs. Fast track and breakthrough therapy programs involve more frequent interactions with FDA or intensive guidance from the agency to facilitate development. The priority review program

involves a shorter goal timeframe for review of a marketing application and does not affect development time. The accelerated approval program is characterized by, among other features, approval of a drug that demonstrates an effect on a surrogate endpoint, or an intermediate clinical endpoint, that is reasonably likely to predict clinical benefit. Of note, while FDA has observed that there may be "fewer, smaller, or shorter clinical trials" for drugs granted accelerated approval, the sponsor must still demonstrate by substantial evidence the safety and effectiveness of the drug. Moreover, the accelerated approval pathway also includes postmarketing study requirements for the sponsor to verify the

anticipated clinical benefit. In the rare cases where clinical benefit is not confirmed post-approval, FDA has the authority to conduct expedited withdrawal of the drug or the indication from the market.

It is also important to recognize that the standards for designation under the breakthrough therapy and fast track programs are not the same as the FDA standards for drug approval. For example, the clinical evidence needed to support breakthrough therapy designation is generally preliminary. In contrast, a more extensive set of data are needed to support approval of a marketing application. Each approval decision must factor in the specific benefits and risks of the proposed drug and its intended use, based on FDA's review of the full data submitted. FDA's approval standards are based on the fundamental statutory requirements, which are therefore not altered by the use of expedited programs.

Oversight of drug safety is a critical component of FDA's public health mission for drugs, both pre-and post-approval. Approved drugs that were the subject of expedited programs do not necessarily require different postmarket safety monitoring than other drugs.

FDA monitors and reviews safety information about all drugs throughout their lifecycles, interacting with sponsors during product development and clinical investigation of the drugs, closely reviewing safety issues during consideration of marketing applications, and, if the drugs are approved, monitoring safety reports after the drugs are marketed.

After drug approval, FDA may learn of new, more serious, or more frequent adverse drug reactions from, for example, post-approval voluntary or mandatory reporting of adverse drug reactions during use of the drug; post-approval clinical trials exploring new uses of the drug; or other post-approval studies, including epidemiologic studies or active surveillance evaluations. The FDA's Center for Drug Evaluation and Research (CDER) integrates what it learns from required sponsor reporting and its own evaluations into an overall system of postmarketing surveillance and risk assessment. The Center then uses this information to take appropriate action when the risks identified indicate a need to provide additional safety information to the public, update drug labeling, require postmarketing studies or trials, require additional risk management interventions, or, on rare occasions, withdraw approval of a drug.

Two of the mechanisms that CDER uses to further evaluate a drug after it has been approved are postmarketing requirements (PMRs) and focused tracking of certain postmarketing safety issues (tracked safety issues or TSIs). Very generally, PMRs are studies or clinical trials that gather additional information about the safety, efficacy, or optimal use of an approved drug, and which sponsors are required to conduct by statute

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or regulation. A PMR can be put in place at the time a drug is approved or any time a new safety issue is identified. TSIs represents those postmarketing safety issues that are considered "significant" according to pre-specified threshold criteria; are entered into

CDER's tracking system¹; and for which multi-disciplinary teams are formed to evaluate the issue and determine the need for regulatory action. This can be put in place at any time once a product is on the market.

These same tools are utilized for drugs that have been the subject of expedited development and review programs and can take into account what was learned during development and the nature of the population to be treated. For example, for drugs granted accelerated approval, PMRs have been required to verify and describe the anticipated clinical benefit, and also yield supplemental postmarket safety information.

FDA conducts rigorous oversight of postmarket safety issues, despite certain challenges related to administrative tracking of postmarket safety work. Through its own processes for continuous improvement, FDA recognized these challenges prior to initiation of the GAO study and is currently addressing those concerns through ongoing improvement efforts.

Tracked Safety Issues

Well before this GAO study, CDER recognized that our administrative tracking of TSIs needed improvement. CDER determined that the number of TSIs entered into its tracking system was low compared the number of postmarketing safety issues already identified and/or under evaluation by CDER staff. However, the work to identify, evaluate, and address postmarketing safety issues was and is being conducted. This is evidenced by the numerous actions FDA has taken to address postmarketing safety issues. For example, in calendar years 2012-2014, labeling changes related to safety

¹ Currently, TSIs are tracked in CDER 's Document Archival, Retrieval and Reporting System (DARRTS).

were made to about 45 approved drug products each month through processes initiated by both FDA and sponsors². Given the high workload of review staff and limited available resources, CDER staff prioritized fully identifying, evaluating, communicating about, and taking appropriate regulatory action to address safety issues, over expending limited resources on entering information about the safety issues into our tracking system. This does not mean that review work undertaken is not being documented; only that it was not documented as formal "tracked safety issues" in CDER's tracking system.

The TSI process is only one of the ways in which information about significant postmarketing safety issues is shared within the Center. CDER also uses complementary mechanisms to track and keep management apprised of postmarketing safety issues.

Examples of these mechanisms include:

- Weekly reports to the Office of New Drugs Senior Management Team, which highlight important post market drug safety issues that have been identified;
- Joint safety meetings between the Office of New Drugs and the Office of Surveillance and Epidemiology (OSE);
- The European Medicines Agency-FDA Pharmacovigilance (EMA-FDA PV) Cluster Meetings; and
- Monthly evaluations by the Division of Clinical Review (DCR) in the Office of Generic Drugs to search and assess the FDA Drug Quality Reporting System (DQRS).

Postmarketing Requirement s and Commitments

FDA has continually worked to improve its ability to maintain accurate and timely data on the status of PMRs and postmarketing commitments (PMCs). A recent internal evaluation of our data, which began in 20 14 and continued into 2015, resulted in updates and corrections to our data, even while GAO was doing its assessment. These activities have resulted in CDER implementing additional oversight mechanisms to ensure the timeliness and accuracy of PMR/PMC data.

² See FDA's MedWatch web page, at <http://www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDruglabelingChanges/default.htm>

Despite the identified challenges with FDA's database on PMRs and PMCs, these data continue to demonstrate that sponsors are conducting their postmarketing studies and trials:

- After completion of the seventh annual review of the "backlog"³ of PMRs and PMCs (as of September 30, 2014), 87% (1,354/1,554) of the PMRs and PMCs in CDER's "backlog" have been closed (i.e., fulfilled or released).
- FDA's most recent annual assessment of the status of PMRs and PMCs overall⁴ found that, as of September 30, 2014, most open PMRs (87% for NDAs and 88% for BLAs) and most open PMCs (68% for NDAs and 77% for BLAs) are progressing on schedule. Thus, at the end of that same fiscal year, only 13% of

the open NDA PMRs were delayed and only 11% of the open BLA PMRs were delayed.⁵

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Ongoing Improvement Efforts

Based on its self-initiated evaluations, HHS has already taken steps to implement new processes and procedures to address the gaps and correct - as indicated - its data on PMRs/PMCs and This. For example, CDER has implemented data entry and tracking procedures and measures to improve available informatics tools to ensure the timeliness and accuracy of its data on the status of PMRs and PMCs. Additionally, CDER has begun to retroactively enter information into its tracking

³ Section 921 of Title IX of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amended section 505(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) by adding a provision requiring the FDA to "on an annual basis, review the entire backlog of postmarketing safety commitments to determine which commitments require revision or should be eliminated, report to the Congress on these determinations, and assign start dates and estimated completion dates for such commitments." The "backlog" consists of all PMRs and PMCs that were open (not yet released or fulfilled) as of the date of enactment of FDAAA. The FDA's seventh annual review of the PMR/PMC "backlog" is available at: [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-market ingPhaseIYCommitments/UCM472973.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Post-market%20ingPhaseIYCommitments/UCM472973.pdf).

⁴ Under section 5068 of the Food, Drug, and Cosmetic Act, the FDA is required to report annually in the Federal Register on the status of postmarketing requirements and commitments required of, or agreed upon by, holders of approved drug and biological products.

⁵ FDA plans to present this information in its forthcoming FY 2014 Federal Register report on the status of postmarketing requirements and commitments.

system about This that were previously identified, evaluated and/or acted upon. Furthermore, CDER is actively engaged in activities to increase and/or streamline the capture of specific information into its tracking system, to facilitate additional analyses for oversight of postmarketing studies and safety issues.

HHS Response to GAO Recommendation

Conducting rigorous oversight of postmarketing safety issues is a priority for HHS, and the agency is committed to completing implementation of measures that advance this priority. Therefore, HHS concurs with GAO's recommendation that FDA establish comprehensive plans to improve processes for capture of PMR/PMC and TSI data, and to correct the identified problems with the data, so that these data can be most effectively used to monitor drugs in the postmarketing setting.

Data Tables

Data Table for Figure 1: Requests the Food and Drug Administration (FDA) Granted and Denied for Fast Track Designation, October 2006 through December 2014

	2007	2008	2009	2010	2011	2012	2013	2014	2015
Granted	60	48	48	65	54	55	77	89	29
Denied	27	25	27	31	30	23	18	22	4

Data Table for Figure 2: Requests the Food and Drug Administration (FDA) Granted and Denied for Breakthrough Therapy Designation, July 9, 2012, through December 31, 2014

	2012	2013	2014	2015
Granted	1	31	31	8
Denied	1	52	51	16

Data Table for Figure 3: Requests for Fast Track Designation That the Food and Drug Administration (FDA) Granted and Denied, by Product Category, October 2006 through December 2014

	Antiviral	Oncology	Neurology	Anti- Infective	Gastroenterology and inborn errors	Cardiovascular and renal	Hematology	All other categories
Granted	112	81	74	55	46	32	34	91
Denied	8	35	17	18	10	19	40	60

Data Table for Figure 4: Requests for Breakthrough Therapy Designation That the Food and Drug Administration (FDA) Granted and Denied, by Product Category, July 9, 2012, through December 31, 2014

	Oncology	Antiviral	Hematology	Pulmonary, allergy and rheumatology	Gastroenterology and inborn errors	Psychiatry	All other categories
Granted	15	14	14	7	5	4	12
Denied	30	5	13	11	3	2	56

Data Table for Figure 5: Drug Applications Approved by the Food and Drug Administration (FDA) That Used at Least One Expedited Program, Categorized by Number of Expedited Programs, October 2006 through December 2014

Number of Expedited Programs (N = 444)

1 expedited program (77%)
2 expedited programs (18%)
3 expedited programs (5%)
4 expedited programs (< 1%)
Total

Data Table for Figure 6: Number of Drug Applications Approved by the Food and Drug Administration (FDA) That Used an Expedited Program, October 2006 through December 2014

	Accelerated approval	Expedited Program - Breakthrough therapy	Expedited Program - Fast track	Priority review
Number of drug applications	50	17	93	408

Data Table for Figure 7: Comparison of New Drug Applications (NDA) for New Molecular Entities (NME) and Non-NMEs, October 2006 through December 2014

NME

	Expedited	Non-Expedited	Total
NME	111	106	217

Non-NME

	Expedited	Non-Expedited	Total
Non-NME	284	1045	1329

Data Table for Figure 8: Number of Drug Applications Approved by the Food and Drug Administration (FDA) That Used at Least One Expedited Program by Product Category, October 2006 through December 2014

Product category	Number of drug applications
Oncology	83
Antiviral	77
Hematology	55
Gastroenterology and inborn errors	35
Psychiatry	31
Anti-Infective	27
All other categories	136

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