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Report to the Chairman, Committee on Health, Education, Labor, and Pensions, U.S. Senate

May 2017

GENERIC DRUG USER FEES

Application Review Times Declined, but FDA Should Develop a Plan for Administering Its Unobligated User Fees

GAO-17-452

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GAO Highlights

Highlights of GAO-17-452, Report to the Chairman, Committee on Health, Education, Labor, and Pensions, U.S. Senate

Why GAO Did This Study

Nearly 90 percent of prescription drugs dispensed in the United States are generic drugs. According to FDA, an increasing volume of generic drug applications over the past decades stressed its ability to review applications efficiently. GDUFA granted FDA the authority to collect user fees from the generic drug industry to supplement resources for the generic drug program. In return, FDA committed to meeting certain performance goals related to the timely review of generic drug applications and to implementing review process improvements.

GAO was asked to examine FDA's implementation of GDUFA. In this report, GAO (1) examines how user fees supported the generic drug program, (2) describes FDA's improvements to the generic drug application review process, and (3) analyzes changes in generic drug application review times. GAO reviewed laws and regulations; FDA policy, guidance, the GDUFA Commitment Letter, and GDUFA financial reports from fiscal years 2013 through 2016; FDA data on application review times from fiscal years 2012 through 2015; and interviewed officials from FDA, generic drug manufacturers, and trade associations.

What GAO Recommends

GAO recommends that FDA develop a plan for administering user fee carryover that includes analyses of program costs and risks and reflects operational needs and contingencies. HHS agreed with GAO's recommendation.

View GAO-17-452. For more information, contact John E. Dicken at (202) 512-7114 or dickenj@gao.gov.

What GAO Found

Since the enactment of the Generic Drug User Fee Amendments of 2012 (GDUFA), the Food and Drug Administration's (FDA) reliance on user fees has increased from $121 million in fiscal year 2013 to $373 million in fiscal year 2016, or 45 percent of total program obligations in fiscal year 2013 to 76 percent in fiscal year 2016. FDA carried over $174 million in unobligated user fees at the end of the fourth year of the GDUFA 5-year period. GAO found that although FDA uses an internal management report to track user fee cash flows for internal purposes, it lacks a plan for administering its carryover—one that includes a fully-documented analysis of program costs and risks to ensure that program operations can be sustained in case of unexpected changes in collections or costs. GAO previously found that it is important for entities with carryover to establish appropriate target amounts based on program needs, risks, and contingencies. FDA's approach is inconsistent with best practices for managing federal user fees. Without a carryover plan, FDA lacks reasonable assurance that the size of its carryover is appropriate to ensure the efficient and responsible use of resources.

Generic Drug User Fee Collections, Obligations, and the Carryover, Fiscal Years 2013 through 2016

Dollars in millions

Fiscal year	Beginning user fee carryover	User fee collections	User fee obligations	Year-end user fee carryover
2013	n/a	$298	$121	$176
2014	$176	$327	$226	$278
2015	$278	$285	$332	$231
2016	$231	$315	$373	$174

Legend: n/a = not applicable

Source: GAO analysis of Food and Drug Administration data. | GAO-17-452.

FDA took steps to improve the timeliness and predictability of generic drug application reviews. FDA restructured the generic drug program by building a more robust organizational infrastructure, upgrading information technology systems, and implementing communication reforms. As FDA implemented these changes, it made additional refinements in response to applicants' feedback.

Generic drug application review times have improved under GDUFA. FDA's review time for a new generic drug application (known as an Abbreviated New Drug Application (ANDA)) decreased from 28 months for applications submitted in fiscal year to 2012 to about 14 months for those submitted in fiscal year 2015. FDA also surpassed multiple GDUFA performance goals. For example, FDA committed to reviewing 60 percent of ANDAs submitted in fiscal year 2015 within 15 months of their receipt. GAO found that FDA had taken action on 89 percent of such ANDAs for which it committed to conducting a substantive review by December 31, 2016, thereby surpassing this goal.

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Abbreviations

ANDA	Abbreviated New Drug Application
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
FDA	Food and Drug Administration
FY	fiscal year (October 1 – September 30)
GDUFA	Generic Drug User Fee Amendments of 2012
HHS	Department of Health and Human Services
HQ	headquarters
IT	information technology
OGD	Office of Generic Drugs
ORA	Office of Regulatory Affairs
PAS	Prior Approval Supplement

U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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May 25, 2017

The Honorable Lamar Alexander
Chairman
Committee on Health, Education, Labor, and Pensions
United States Senate

Dear Mr. Chairman:

Nearly 90 percent of prescription drugs dispensed in the United States are generic drugs. A generic drug is essentially a copy of an approved brand-name drug.[1] They typically have the same active ingredients, strength, dosage form, route of administration, and intended conditions of use as their brand-name counterparts but generally cost less, yielding savings for consumers and public and private health plans. Generic drugs become available to consumers when brand-name drugs' patents and other periods of market exclusivity expire and generic manufacturers obtain approval to market their drugs.[2] The Food and Drug Administration (FDA) within the Department of Health and Human Services (HHS) is responsible for protecting the public's health by overseeing the safety, effectiveness, and quality of domestic and imported pharmaceutical products marketed in the United States, including generic drugs.[3] The generic drug industry's rapid global expansion in the past several decades has resulted in an increase in the volume of generic drug applications submitted to FDA for scientific review and approval and the number of manufacturing facilities in need of inspection. FDA officials

[1]A brand-name drug is a drug marketed under a proprietary, trademark protected name.

[2]Patents are issued by the U.S. Patent and Trademark Office, generally for a term of 20 years from the date of filing. A patent on the process of manufacturing a drug grants its owner the right to exclude others from making, using, selling, offering to sell, or importing the patented invention into the United States. See 35 U.S.C. § 154(a). In the case of drugs, the patent protects the investment in a new drug's development by giving the manufacturer the sole right to sell the drug while the patent is in effect.

[3]FDA oversees generic drugs, in part, by reviewing and approving applications for all generic drugs before they can be marketed to consumers. As part of the approval, FDA inspects establishments that play a role in manufacturing the drug.

For this report, we use the term "generic drug program" to refer to FDA's human generic drug program. We also use the term "applications" to refer to generic drug applications that are submitted to FDA by applicants seeking approval to market generic drug products in the United States.

have stated that this growth stressed FDA's ability to review applications efficiently.

To address these issues, Congress passed, and the President signed into law, the Generic Drug User Fee Amendments of 2012 (GDUFA), which provided additional resources to facilitate FDA's review of generic drug applications in less time.[4] GDUFA granted FDA the authority to collect approximately $1.5 billion in user fees from the generic drug industry over a 5-year period to supplement FDA's regular appropriations for the agency's generic drug program.[5] In return, FDA committed to implementing program enhancements and meeting certain performance goals related to the review of applications, which are intended to improve the efficiency, quality, and predictability of generic drug program activities that, in turn, could accelerate FDA's review of generic drugs. In 2013, FDA negotiated certain commitments with industry that were transmitted to Congress in a Commitment Letter. The Commitment Letter, which covers the 5-year period, includes GDUFA performance goals, as well as user fee collection amounts that were negotiated between FDA and industry stakeholders (e.g., manufacturer associations and individual

[4]Pub. L. No. 112-144, § tit. III, 126 Stat. 993, 1008 (2012) (codified at 21 U.S.C. § 379f *et seq.*).

[5]User fees are fees assessed to users for goods or services provided by the federal government. GDUFA requires FDA to collect generic drug user fees and specifies that FDA shall establish fees to generate a total estimated revenue amount equal to $299 million, adjusted for inflation, for each fiscal year from 2013 through fiscal year 2017. Fees are collected and available for obligation only to the extent and in the amount provided in advance in appropriations acts. An agency incurs an obligation, for example, when it places an order, signs a contract, awards a grant, purchases a service, or takes other actions that require the government to make payments to the public or from one government account to another. For fiscal year 2016, Congress appropriated $318 million in generic drug user fees for collection and obligation—the total amount authorized under GDUFA. Consolidated Appropriations Act, 2016, Pub. L. No. 114-113, div. A, 129 Stat. 2242, 2269 (2015). For our purposes, we use the term "regular appropriations" to refer to annual, non-user fee appropriations—the funding provided to FDA in advance in appropriations acts.

companies).[6] FDA's authority to collect user fees for generic drugs will expire on October 1, 2017, and GDUFA will need to be reauthorized in order for FDA to continue to collect user fees on generic drugs.

You asked us to examine FDA's implementation of GDUFA and its impact on application review times. This report addresses

1. how FDA used generic drug user fees to support the generic drug program;
2. FDA's efforts to improve the generic drug application review process; and
3. how, if at all, FDA's review times for generic drug applications changed since the enactment of GDUFA.

You also asked us to provide information on regulatory science research priorities that support the development of generic drugs. Appendix I includes a discussion of regulatory science and lists regulatory science research projects funded by GDUFA.

To examine how generic drug user fees were used by FDA to support the generic drug program, we reviewed relevant laws and regulations; FDA policy and guidance documents; agency presentations to the generic drug industry; and reports on agency and program appropriations and generic drug user fees, such as FDA's budget justification reports and GDUFA financial reports. We interviewed FDA officials about user fee collections, allocations, obligations, and carryover amounts, including the methods used to plan for and record financial decisions. We analyzed financial data and information provided by FDA that disclosed allocations and obligations for the generic drug program from fiscal years 2013 through

[6]The user fee commitments contain performance goals for FDA's generic drug review activity for fiscal years 2013 through 2017, such as reviewing and acting upon a certain number of generic drug applications within certain time frames. Upon negotiating these commitments with industry, the Secretary of Health and Human Services submitted a letter to Congress outlining these performance goals. Pub. L. No. 112-144, § 301(b), 126 Stat. at 1008 (codified as a note at 21 U.S.C. § 379j-41). Most of the goals began in fiscal year 2015, the third year of the program. See http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf (accessed May 17, 2017). For each fiscal year of the user fee program, FDA is required to submit a report on its progress in achieving the goals outlined in the Commitment Letter and future plans for meeting them. 21 U.S.C. § 379d-4(a). In this report, references to the "Commitment Letter" are to the generic drug user fee commitment letter submitted to Congress.

2016.[7] We compared FDA documents and practices to findings from our prior work on managing and evaluating user fees and to federal internal control standards.[8] We assessed the reliability of FDA data we received by reviewing related documentation, performing data reliability checks (such as examining the data for missing values and checking values against other documentation), and interviewing relevant agency officials with knowledge of the generic drug program and how user fees are being used. On the basis of these steps, we determined that the data were sufficiently reliable for the purposes of our reporting objectives.

To describe FDA's efforts to improve its generic drug application review process, we reviewed relevant laws, agency policies, procedures, and regulations, as well as other relevant reports and guidance documents. We interviewed FDA officials about their improvement initiatives and also interviewed representatives from the generic drug industry to obtain their perspectives. Specifically, we interviewed officials from five trade associations that represent various aspects of generic drug manufacturing, as well as six generic drug manufacturing companies, to obtain a wide range of stakeholder perspectives about FDA's implementation of GDUFA.[9] We selected manufacturers that varied in terms of the number of generic drug application submissions and approvals since the implementation of GDUFA. All selected trade associations participated in meetings held by FDA to discuss the reauthorization of the generic drug user fee program. To describe steps FDA has taken to address industry concerns about changes made to the

[7]An obligation refers to a definite commitment that creates a legal liability of the government for the payment of goods and services ordered or received. For more information on budget terminology, see GAO, *A Glossary of Terms Used in the Federal Budget Process*, GAO-05-734SP (Washington, D.C.: September 2005).

[8]See GAO, *Federal User Fees: Fee Design Options and Implications for Managing Revenue Instability*, GAO-13-820 (Washington, D.C.: Sept. 30, 2013); and *Budget Issues: Key Questions to Consider When Evaluating Balances in Federal Accounts*, GAO-13-798 (Washington, D.C.: Sept. 30, 2013). See also GAO, *Standards for Internal Control in the Federal Government*, GAO-14-704G (Washington, D.C.: September 2014). Internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved.

[9]We interviewed officials from the Bulk Pharmaceuticals Task Force, the Generic Pharmaceutical Association (renamed the Association for Accessible Medicines), the International Pharmaceutical Excipients Council of the Americas, the Pharma-Biopharma Outsourcing Association, and the Specialty Pharma Association.

generic drug application review process, we examined FDA documents and interviewed FDA officials.

To examine whether FDA's review times for generic drug applications have changed, we examined FDA data on generic drug submissions for fiscal years 2012 through 2015 that FDA determined were sufficiently complete to permit a substantive review to identify trends in FDA's review times for generic drug applications.[10] Our analysis focused on FDA's time for completing the first review cycle.[11] We also reviewed the GDUFA performance goals outlined in FDA's Commitment Letter to Congress, examined FDA's performance reports to Congress, and analyzed FDA data to assess whether FDA met its GDUFA performance goals for fiscal year 2015. Specifically, we analyzed the proportion of sufficiently complete generic drug applications and the proportion of communications for which FDA met or did not meet the applicable performance goal.[12] We reviewed the data for reasonableness and consistency, including screening for missing data, outliers, and obvious errors. We also interviewed FDA officials about steps the agency has taken to ensure data reliability. On the basis of these steps, we determined that the data were sufficiently reliable for the purposes of our reporting objectives.

We conducted this performance audit from April 2016 through May 2017 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.

[10]FDA requires applications to be sufficiently complete to conduct a substantive review and will issue a refusal to receive letter when it determines that an application is not sufficiently complete to permit such a review. We did not include these applications in our analyses of completed applications.

[11]The first review cycle begins when FDA receives an application from a generic drug applicant and ends when FDA issues an action letter that informs the applicant of the agency's decision about an application. If FDA does not approve the application during the first review cycle, it issues a letter describing any problems identified in the application that prevented it from being approved. A new review cycle begins if the applicant resubmits the application to FDA. Our analysis did not include any such subsequent reviews in calculating FDA's review time.

[12]FDA's issuance of a refuse to receive letter counts toward meeting applicable GDUFA performance goals. However, we did not include these applications in our analyses.

Background

FDA's Generic Drug Program Organization

Four components within FDA have primary responsibility for ensuring the safety and effectiveness of generic drugs. Among other activities, these components evaluate the safety and effectiveness of generic drugs prior to marketing, monitor the safety and effectiveness of marketed products, oversee the advertising and promotion of marketed products, formulate regulations and guidance, set research priorities, and communicate information to industry and the public.

- **The Center for Drug Evaluation and Research (CDER)** is responsible for overseeing drugs and certain therapeutic biologics. It coordinates federal government efforts to ensure the safety and efficacy of generic drugs as well as new and over-the-counter drugs.
- **The Center for Biologics Evaluation and Research (CBER)** is responsible for overseeing generic drug applications for biologics, which are products such as blood, vaccines, and human tissues. These products make up a smaller proportion of the generic drug applications than those reviewed by CDER.
- **The Office of Regulatory Affairs (ORA)** is responsible for conducting field activities for all of FDA's medical product centers, which include CDER and CBER, such as inspections of domestic and foreign establishments involved in manufacturing medical products.
- **FDA headquarters (HQ)**, specifically the Office of the Commissioner, includes several offices that perform a variety of activities that contribute to indirect costs related to the GDUFA program. FDA HQ provides agency level shared services; policy, financial, and legal support; and other overhead support that is provided to all FDA programs and activities.

Within CDER, the Office of Generic Drugs (OGD) is responsible for providing regulatory oversight and strategic direction for FDA's generic drug program to expedite the availability of safe, effective, and high-quality generic drugs to patients. These activities include reviewing generic drug applications, which comprises such actions as examining bioequivalence data and evaluating proposed drug labeling.[13] In addition,

[13]A generic drug is considered to be bioequivalent to the brand-name drug if (1) the rate and extent of absorption of the drug do not show a significant difference from the brand-name drug; or (2) where there is an intentional difference in rate, there is no significant difference in the extent of absorption and any difference is not medically significant.

the Office of Pharmaceutical Quality, also within CDER, is responsible for examining chemistry-related data and providing quality control across all manufacturing sites, whether domestic or foreign, across all drug product areas.

Generic Drug Review Activities

FDA begins review of a generic drug when a generic drug applicant submits an Abbreviated New Drug Application (ANDA). Generic drug applications are termed "abbreviated" by FDA because they are generally not required to include preclinical study data (studies involving animals) and clinical trial data (studies involving humans) to establish safety and effectiveness. Because generic drugs must be bioequivalent to a brand-name drug already approved by the FDA, and because animal studies and clinical trials have already been conducted for the brand-name drug, generic drug applicants do not need to repeat these animal or human studies.

FDA's approval of a drug's application is required before a generic drug can be marketed for sale in the United States.[14] FDA will meet the performance goals outlined in its Commitment Letter when it completes its review and issues an action letter for a specified percentage of applications within a designated period of time. An action letter is an official statement informing a drug applicant of the agency's decision about an application review. FDA can issue four types of action letters:

- **Refuse to receive letter:** FDA issues a refusal to receive letter when it determines that an application is not sufficiently complete to permit a substantive review.
- **Approval letter:** FDA issues an approval letter to an applicant when the agency has concluded its review of a generic drug application and the applicant is authorized to commercially market the drug.
- **Tentative approval letter:** FDA issues a tentative approval letter when the agency has completed its review of an application, but patents or other exclusivities for the original, brand-name product prevent approval. A tentative approval letter does not allow the applicant to market the generic drug product until the related patents and other exclusivities no longer prevent approval.
- **Complete response letter:** FDA issues a complete response letter to an applicant at the completion of a full application review where

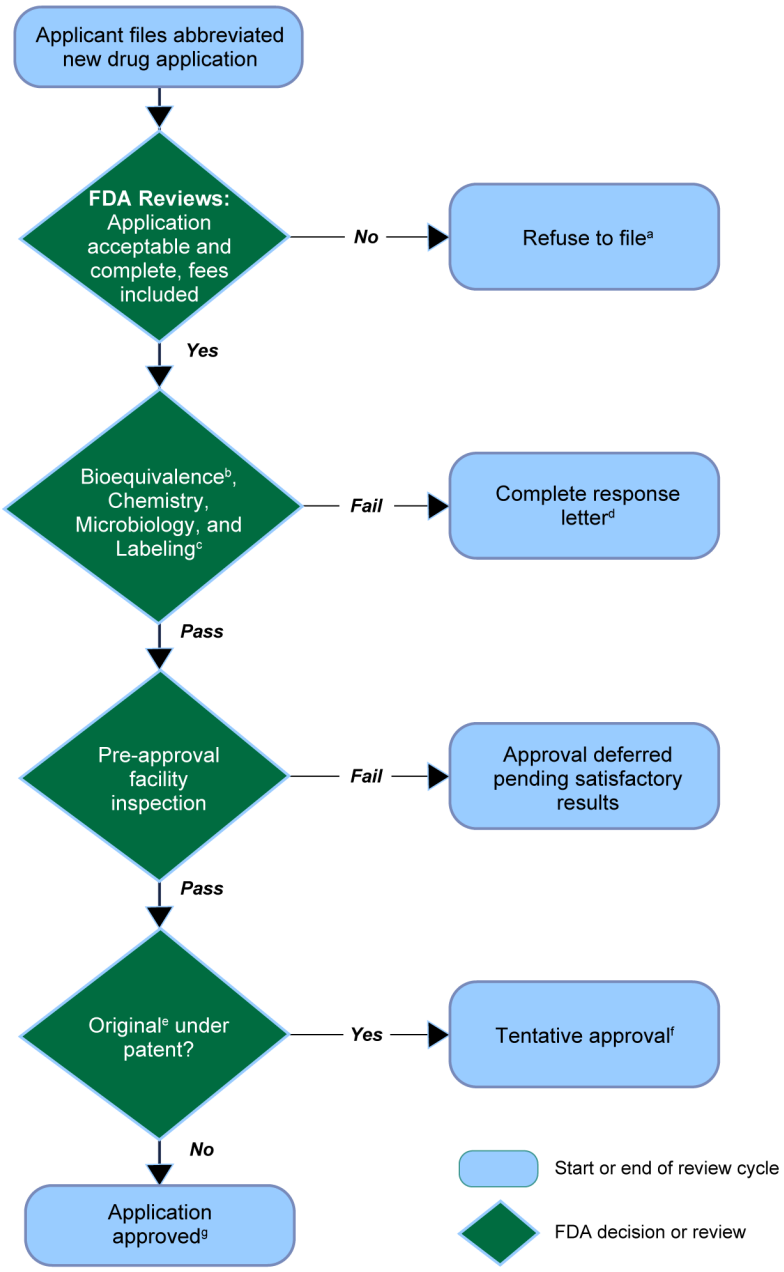
[14] 21 U.S.C. § 355(a).

deficiencies are found—the complete response letter describes any deficiencies that must be corrected in order for an application to be approved.

In order to close the review cycle, FDA must complete its review and issue an approval, tentative approval, or a complete response letter.[15] If the agency has not issued one of these letters, the application is considered a pending application. (See fig. 1 for a summary of the generic drug application review process.)

[15]The review cycle is also closed if, at the outset of the review process, FDA refuses to receive an ANDA that is incomplete (i.e., issues a refuse to receive letter). A review cycle can also be closed if an applicant withdraws the application.

Figure 1: FDA's Generic Drug Application Review Process



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-17-452

Note: FDA reviews of bioequivalence, chemistry, microbiology, and labeling and pre-approval facility inspection may occur concurrently.

[a]Refuse to receive letter: FDA issues a refusal to receive letter when it determines that an application is not sufficiently complete to permit a substantive review.

[b]Bioequivalence: A generic drug is considered to be bioequivalent to the brand-name drug if (1) the rate and extent of absorption of the drug do not show a significant difference from the brand-name drug; or (2) where there is an intentional difference in rate, there is no significant difference in the extent of the absorption and any difference is not medically significant.

[c]Labeling: Labeling includes the container labels, package insert (or professional labeling), the patient package insert, medication guides, instructions for use, risk management materials and promotional labeling.

[d]Complete response letter: FDA issues a complete response letter to an applicant at the completion of a full application review where deficiencies are found—the complete response letter describes any deficiencies that must be corrected in order for an application to be approved.

[e]"Original" refers to the approved drug product upon which an applicant relies in seeking approval of its generic drug application.

[f]Tentative approval letter: FDA issues a tentative approval letter when the agency has completed its review of an application, but patents or other exclusivities for the original, brand-name product prevent approval. A tentative approval letter does not allow the applicant to market the generic drug product until the related patents and other exclusivities no longer prevent approval.

[g]Application approval: FDA issues an approval letter to an applicant when the agency has concluded its review of a generic drug application and the applicant is authorized to commercially market the drug.

Once an ANDA is filed, an FDA review team—medical doctors, chemists, statisticians, microbiologists, pharmacologists, and other experts—evaluates whether scientific data in the application demonstrates that the drug product meets the statutory and regulatory standards for approval. For example, applicants must, in most cases, demonstrate that the generic product, in relation to an already-approved brand-name drug

- contains the same active ingredient(s);
- is identical in strength, dosage form, and route of administration;
- is labeled for conditions of use approved for the brand-name drug;
- is bioequivalent to an already-approved brand-name drug;
- meets the same requirements for identity, strength, purity, and quality; and
- is manufactured under the same strict standards of FDA's good manufacturing practice regulations required for brand-name products.[16]

[16]The statute permits the generic product to deviate from the brand-name drug in certain respects if FDA has approved a suitability petition permitting the deviations. See 21 U.S.C. § 355(j)(2)(c); 21 CFR § 314.93 (2016).

The application must also contain information to show that, with permitted deviations, it has the same labeling as the brand-name product.

FDA communicates with applicants when issues arise during its review of an application that may prevent the agency from approving the application.[17] In response, applicants can submit additional information to FDA in the form of amendments to the original application. FDA review time for an original application (i.e., the first review cycle) is calculated as the time elapsed from the date FDA receives the application and associated user fee to the date it issues an action letter. The application review process will also be closed if the application is withdrawn by the applicant. The date on which one of these actions occurs is used to determine whether the review cycle was completed within FDA's committed time frames. If FDA issues a complete response letter listing the deficiencies in the application that were encountered by FDA's reviewers, the applicant may choose to submit a revised application to FDA. Resubmissions and their review are covered under the user fee paid with the original submission, but a new review cycle with its own performance goals is started.

If an applicant wants to change any part of its original ANDA after its approval—such as changes to the manufacturing location or process, the type or source of active ingredients, or the labeling—it must submit an application supplement to notify FDA of the change.[18] If the change has a substantial potential to adversely affect factors such as the identity, quality, purity, or potency of the drug, the applicant must obtain FDA approval for the change through submission of a Prior Approval Supplement (PAS).[19]

Outside of the application review process, FDA also responds to correspondence submitted to the agency by, or on behalf of, an applicant

[17]For example, FDA will issue a letter to applicants to inform them of any issues with the filing of their application that were identified during FDA's initial review of a generic drug application. Additionally, approximately midway through its review of a drug application, applicants can request status updates on their applications.

[18]21 C.F.R. §§ 314.70, 314.97 (2016).

[19]21 C.F.R. § 314.70(b) (2016). See also Food and Drug Administration, Center for Drug Evaluation and Research, *Guidance for Industry: Changes to an Approved NDA or ANDA*, April 2004, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM077097.pdf (accessed May 17, 2017).

requesting information on a specific element of generic drug product development. This communication between FDA and applicants, known as controlled correspondence, allows applicants to submit formal questions seeking the agency's input on issues capable of affecting the review of a product prior to their submission of an ANDA.

Funding for the Generic Drug Program

The generic drug program is supported by both regular appropriations and generic drug user fee appropriations. Generic drug user fees provide funds to FDA to support its efforts to review applications for generic drugs in a timely manner. GDUFA authorizes FDA to collect from the generic drug industry $299 million in user fees annually through September 30, 2017, adjusted for inflation, to supplement the regular appropriations the agency receives to support the generic drug program. GDUFA established several types of fees associated with generic drug products that together generate the annual collections. These include fees for (1) ANDAs in the backlog as of October 1, 2012 (assessed in fiscal year 2013 only); (2) ANDAs and PASs submitted after October 1, 2012; (3) facilities where active pharmaceutical ingredients and finished dosage forms are produced; and (4) Drug Master Files that are associated with generic drug products.[20] Although GDUFA authorizes FDA to collect user fees, the law specifies that the total amount of user fees collected for a fiscal year be provided in appropriations acts.[21] FDA establishes the generic drug user fee collection amounts annually to generate revenue levels as specified in appropriations acts.[22] Once appropriated and collected, user fees are available for obligation by FDA until expended. As

[20]A Drug Master File is a submission to FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. Among other uses, the information contained in a Drug Master File may be used to support an ANDA or PAS.

[21]In addition, GDUFA specifies that, in order for FDA to obligate the user fees it collects, annual appropriations for salaries and expenses of the FDA in each fiscal year the user fee program is in effect must equal or exceed the amount appropriated for fiscal year 2009, multiplied by an adjustment factor. If they are not, GDUFA requires that the fees be refunded. FDA also must allocate at least $97 million of its annual non-user fee appropriation, multiplied by an adjustment factor, for generic drug activities. 21 U.S.C. § 379j-42(h).

[22]FDA's annual user fee funding is derived from broad funding estimates of the number of ANDAs, PASs, and Drug Master Files being submitted. For example, FDA estimates that approximately 750 ANDAs will be submitted each year and uses this estimate to establish its annual user fee collection amounts. However, the number of submissions has varied considerably. In fiscal year 2014, about 1,600 ANDAs were submitted to FDA for approval followed by about 500 the next fiscal year.

a result, any user fees not obligated in the fiscal year in which they were appropriated and collected may be carried over into subsequent fiscal years (referred to as a carryover). In addition, GDUFA specifies that user fees may be spent only for generic drug activities, including the costs of reviewing and approving generic drug applications.[23]

Each year as part of the annual appropriations process, FDA develops and submits supporting information for its funding request, which includes user fee and non-user fee funds, in the budget justification that is submitted to the congressional appropriations committees. This information reflects how FDA proposes to meet its mission, goals, and objectives, and it assists Congress in determining how much funding to appropriate for FDA. This information also includes an estimate of how many generic drug applications are likely to be received in the coming year.

GDUFA Reporting Requirements and Reauthorization

Authority for the generic drug user fee program established under GDUFA expires at the end of fiscal year 2017. During the 5-year period of the current authorization, FDA has been required to submit two annual reports to its oversight committees: (1) a report on the progress made and future plans toward achieving the performance goals identified in its Commitment Letter, and (2) a report on the financial aspects of FDA's implementation efforts. These reports contain descriptions of relevant oversight activities over the previous year, data on FDA's performance toward meeting the commitments, and information about how FDA addressed the implementation and use of the user fees over the previous year.[24]

In addition, to facilitate Congress's reauthorization of the program, GDUFA requires FDA to develop recommendations to present to Congress with respect to the goals, and plans for meeting those goals, during fiscal year 2017 through fiscal year 2022.[25] FDA is to develop

[23]21 U.S.C. §§ 379j-41(8), 379j-42(i).

[24]See, for example, Food and Drug Administration, *FY 2016 Performance Report to Congress for the Generic Drug User Fee Amendments* (Silver Spring, Md.: 2016), and Food and Drug Administration, *FY 2016 GDUFA Financial Report Required by the Generic Drug User Fee Amendments of 2012*.

[25]GDUFA required FDA to transmit these recommendations to Congress by January 15, 2017. 21 U.S.C. § 379j-43(d)(5).

these recommendations in consultation with various stakeholders, including the generic drug industry. FDA and generic drug industry stakeholders conducted negotiations regarding the program's reauthorization, which is referred to as GDUFA II, in October 2015 through August 2016.[26] According to FDA, the negotiated objectives of GDUFA II differ from the objectives of the original GDUFA agreement (i.e., GDUFA I). While the primary objective of GDUFA I was to restructure FDA's generic drug program to improve the speed and predictability of reviews, the primary objective for GDUFA II, as outlined in the proposed Commitment Letter negotiated by FDA and the generic drug industry, is to improve the completeness of drug application submissions and reduce the number of review cycles. Other features include enhanced review pathways for complex drugs, enhanced accountability and reporting, and modifications to the user fee structure.

GDUFA Increased Generic Drug Program Resources Significantly, but the Agency Lacks a Plan for Administering Its Carryover

GDUFA supported an 85 percent increase in total FDA obligations for its generic drug program in the first 4 years of implementation. User fees primarily supported generic drug application evaluation and review activities. FDA has accumulated carryover balances from unobligated user fee collections, but it lacks a plan for administering the carryover, which is inconsistent with best practices identified in our prior work on the management of user fees and federal internal control standards.

User Fees Supported an 85 Percent Increase in Generic Drug Program Obligations, Increasing FDA's Reliance on Such Fees During the Implementation Period

Total obligations for FDA's generic drug program (from both regular appropriations and generic drug user fee appropriations) increased by about 85 percent in the 4 years following GDUFA's implementation, from about $267 million in fiscal year 2013 to about $494 million in fiscal year 2016. (See table 1.) FDA's reliance on generic drug user fees increased throughout this period. Obligations from generic drug user fees grew in both absolute terms and as a share of total program obligations, from about $121 million (45 percent of total obligations) in fiscal year 2013 to about $373 million (76 percent of total obligations) in fiscal year 2016. In contrast, obligations from regular appropriations decreased as a share of

[26]The resulting agreement is available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf (accessed Feb. 2, 2017).

total program obligations during this period, and while these regular appropriations increased in absolute terms from fiscal years 2013 to 2014, they declined afterwards.

Table 1: Generic Drug Program Obligations by Source, Amount, and Percentage of Total Funding, Fiscal Years (FY) 2013 through 2016

Dollars in millions

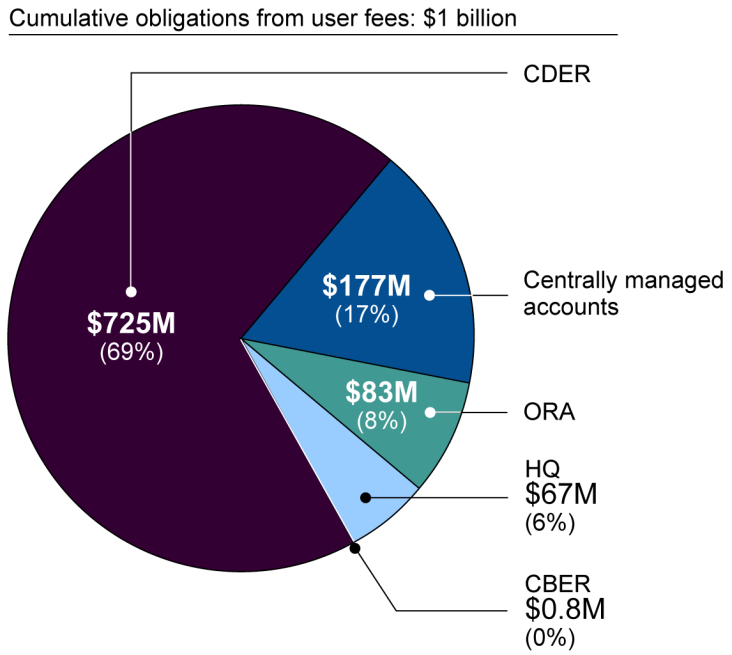
Source of obligations	FY 2013	FY 2014	FY 2015	FY 2016
Regular (non-user fee) appropriations	$146 (55%)	$161 (42%)	$121 (27%)	$121 (24%)
User fees	$121 (45%)	$226 (58%)	$332 (73%)	$373 (76%)
Total obligations from regular and user fee appropriations combined	**$267**	**$387**	**$453**	**$494**

Source: GAO analysis of Food and Drug Administration data. | GAO-17-452

User Fees Primarily Supported Generic Drug Evaluation and Review Activities

In the first 4 years of the generic drug user fee program, FDA obligated over $1 billion (about 70 percent) of the anticipated 5-year, $1.5 billion in user fee collections. CDER, the office with responsibility for drug evaluations and generic drug submission reviews, obligated the largest share of user fees—almost 70 percent—while the three other FDA components with responsibility for the generic drug program obligated smaller shares. Figure 2 shows cumulative user fee obligations by each FDA component and account in fiscal years 2013 through 2016. According to FDA officials, the percentage of user fees allocated to each of these four components did not vary much from year to year. However, FDA officials also reported that each year the agency allocated a percentage of the user fees to centrally managed accounts that are used for rent, utility costs, telecommunications, and other support costs such as information technology (IT) investments that support FDA programs and activities, but which do not necessarily align with the four offices supporting the generic drug program. User fee obligations from the centrally managed account were the second largest component of such obligations each fiscal year since the implementation of GDUFA, trailing only CDER.

Figure 2: Cumulative User Fee Obligations for the Generic Drug Program by FDA Component or Account, Amount, and Percent of Total User Fee Obligations, Fiscal Years 2013 through 2016



Center for Drug Evaluation and Research (CDER)
Office of Regulatory Affairs (ORA)
FDA Headquarters (HQ)
Center for Biologics Evaluation and Research (CBER)

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-17-452

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

In addition, approximately 60 percent of cumulative user fee obligations supported non-personnel activities and about 40 percent supported personnel-related activities, such as employee salaries and benefits, in the first 4 years of GDUFA's implementation (see table 2).[27] In addition to IT investments and capital asset purchases, CDER also obligated funds for non-personnel activities such as consulting services to integrate GDUFA requirements into its new IT system and regulatory science

[27]Non-personnel activities include those with large upfront costs such as implementing changes to the program's organizational structure, improving business processes, purchasing specialized lab equipment, upgrading the IT system, and making other capital asset purchases, some of which required initiating new contracts. Personnel activities include employee salaries and benefits as a direct result of hiring to meet GDUFA goals.

projects with the potential to improve the development of generic drugs. (See Appendix I for more information on GDUFA-supported regulatory science projects.)

Table 2: Generic Drug User Fee Obligations for Non-Personnel and Personnel-Related Activities, by Amount and Percent of Total Program Obligations, Fiscal Years (FY) 2013 through 2016

Dollars in millions

	FY 2013	FY 2014	FY 2015	FY 2016	Cumulative user fee obligations
Obligations for non-personnel activities[a]	$104 (86%)	$154 (68%)	$194 (58%)	$192 (51%)	$644 (61%)
Obligations for personnel–related activities[b]	$18 (14%)	$72 (32%)	$138 (42%)	$181 (49%)	$408 (39%)
Total user fee obligations	**$121**	**$226**	**$332**	**$373**	**$1,052**

Source: GAO analysis of Food and Drug Administration data. | GAO-17-452

Note: Sums may not equal totals due to rounding to nearest whole numbers.

[a]Non-personnel activities include those with large upfront costs such as implementing changes to the program's organizational structure, improving business processes, purchasing specialized lab equipment, upgrading the information technology systems, and making other capital asset purchases.

[b]Personnel-related activities include employee salaries and benefits as a direct result of hiring to meet Generic Drug User Fee Amendment of 2012 goals.

User fee obligations for personnel-related activities increased from fiscal year 2013 to fiscal year 2016, both in absolute numbers and as a percentage of total user fee obligations. Personnel-related obligations increased sharply in the first 4 years of GDUFA, from about $18 million (14 percent) of all user fees obligated in fiscal year 2013, to about $181 million (49 percent) in fiscal year 2016. According to FDA officials, the increase in personnel-related spending was due, in part, to hiring for the generic drug program consistent with the agency's GDUFA goals.[28]

[28]In the Commitment Letter, FDA identified its goal to hire new staff to support the generic drug program by the end fiscal year 2015, incrementally hiring at least 25 percent in fiscal year 2013; 50 percent in fiscal year 2014; and another 25 percent in fiscal year 2015, as necessary to achieve GDUFA's performance metrics and goals. By 2015, FDA had hired nearly 1,200 employees with user fee funds to support the generic drug program.

FDA Accumulated a User Fee Carryover from Unobligated Collections but Lacks a Plan on How it Will Administer the Carryover

FDA has accumulated a large unobligated user fee carryover balance, which it uses as an operating reserve. At the beginning of fiscal year 2017, FDA had a carryover of approximately $174 million. During the first two years of GDUFA's implementation, FDA had obligated about half of the user fees it had collected and thereby amassed a cumulative carryover of about $278 million by the end of fiscal year 2014—an amount nearly as great as the annual, inflation-adjusted user fee collection amount of $299 million.[29] In fiscal years 2015 and 2016, FDA's program obligations from user fees exceeded the amount collected and FDA used part of the carryover to make up for the gap. (See table 3.) In fiscal year 2015, FDA obligated about $47 million from its carryover in addition to its total generic drug user fee appropriation for that year, and in fiscal year 2016, the agency obligated about $58 million from its carryover in addition to its total generic drug user fee appropriation for that year, yielding a carryover balance of about $174 million.

Table 3: Generic Drug User Fee Collections, Obligations, and Carryover, Fiscal Years 2013 through 2016

Dollars in millions

Fiscal year	Beginning user fee carryover	User fee net collections[a]	User fee obligations	Year-end user fee carryover
2013	n/a	$298	$121	$176
2014	$176	$327	$226	$278
2015[b]	$278	$285[b]	$332	$231
2016	$231	$315	$373	$174

Legend: n/a = not applicable.

Source: GAO analysis of Food and Drug Administration data. | GAO-17-452

Note: The Generic Drug User Fee Amendments of 2012 specifies the total amount FDA is allowed to collect each fiscal year, and these funds are available for obligation to the extent and in the amount provided in advance in appropriations acts. User fee collections are reported in the year the fee was originally due, even if the fee is received in a different fiscal year. User fee collection and carryover totals reported for each fiscal year are net of any refunds for the fiscal year and include updated user fee collections from receivables. FDA updates their reported net collections every year.

[a]Net collections include the amount of user fees collected net of any refunds, accounts receivable, or other adjustments that occurred during each fiscal year.

[29]Generic drug user fees that were collected and not obligated at the end of the fiscal year are referred to as carryover and are available solely for generic drug activities and for obligation in future fiscal years. The carryover enables FDA to align fees and costs over a longer period of time and to better prepare for, and adjust to, fluctuations in collections and costs.

[b]Fiscal year 2015 user fee collections decreased by about $38 million primarily due to decreases in the number of Drug Master File and application filing fee collections.

Despite the large carryover amounts, FDA has not developed a planning document on how it will administer its carryover—one that includes a fully documented analysis of program costs and risks to ensure that its carryover reflects expected operational needs and probable contingencies. Although FDA uses an internal management report to show GDUFA collection amounts, obligations, and end-of-year carryover amounts, the agency was unable to produce evidence describing whether the carryover of $174 million at the beginning of fiscal year 2017 (or carryover amounts in other years) was within a targeted goal, and it does not have targets for future years in general. We have previously found that when unobligated balances are used as carryover, it is important for entities to establish a target range for the carryover to ensure user fee resources are used efficiently and responsibly and that the amounts carried over into the following year are reasonable to meet program needs, risks, and probable contingencies.[30] In addition, the lack of such a planning document is inconsistent with federal internal control standards, which state that management should have a control system in place to communicate necessary quality information externally to help the agency achieve its objectives and address related risks.[31]

During GDUFA II negotiations, FDA officials acknowledged the need for more fiscal transparency and accountability and announced plans to build financial systems to facilitate operational and fiscal efficiency and reporting. However, agency officials also stated that their internal management report, which is used to report its user fee cash flows, was sufficient to analyze the program's needs. By not developing a planning document FDA cannot effectively communicate to external stakeholders the amount of its carryover balance and its plans for using it. These external stakeholders include Congress, which determines the total amount of generic drug user fees FDA is to collect through the annual appropriations process. Likewise, Congress also considers GDUFA reauthorization levels based on recommendations that FDA is to develop in consultation with other external stakeholders, who do not have access to FDA's internal reports.

[30]GAO-13-820 and GAO-13-798.

[31]GAO-14-704G.

FDA Implemented Various Changes to Improve the Generic Drug Application Process and Made Additional Refinements in Response to Applicant Concerns

FDA has made changes to the generic drug program since the enactment of GDUFA in order to establish a better-managed drug application review process. In response to stakeholder input, FDA incorporated additional changes to the application review process.

FDA Made Changes to Its Organizational Infrastructure, Information Technology, and Communication Processes

Key changes to FDA's generic drug review process have included revising its organizational infrastructure, upgrading IT, and formalizing external communication processes.

Organizational Infrastructure

To enable FDA to meet the evolving needs of application review and GDUFA performance goals, the agency undertook steps to reorganize OGD in December 2013. Specifically, under this reorganization OGD was elevated to the status of a "super office" within CDER, providing OGD with centralized administrative support and its own governance structure.[32] Under the reorganization, OGD was given the responsibility to coordinate and manage the application review process; provide safety, surveillance, clinical, and bioequivalence reviews for generic products; and develop policy and regulatory science for generic drugs. Four subordinate offices within OGD were created to fulfill these responsibilities: the Office of Research and Standards, the Office of Bioequivalence, the Office of Regulatory Operations, and the Office of Generic Drug Policy. Additionally, in January 2015 FDA established a new Office of Pharmaceutical Quality—another "super office" within CDER—to provide better alignment among all drug quality review

[32]According to FDA officials, a "super office" is an office within CDER that houses subordinate offices within its organizational structure and that reports directly to CDER's Director.

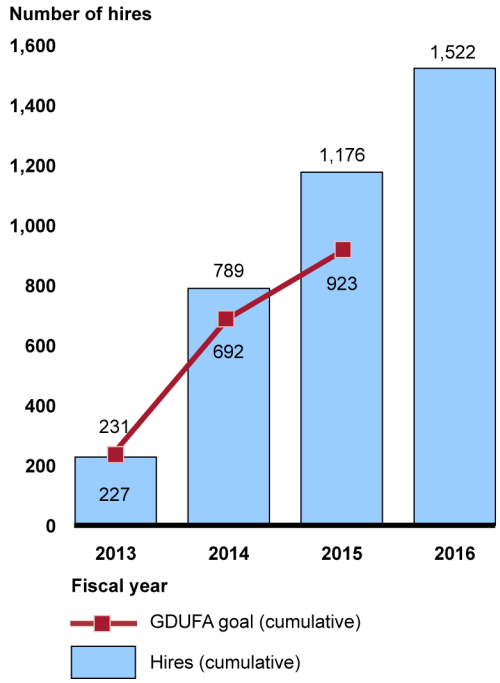
functions, including application reviews, inspections, and research.

As part of its GDUFA hiring goals, FDA planned to hire approximately 923 new staff by the end of fiscal year 2015 and to this end established incremental goals to hire 231 (25 percent), 462 (50 percent), and 231 (25 percent) of the 923 total new staff during the first 3 fiscal years of the program, respectively. However, FDA surpassed the targeted goal in total, hiring nearly 1,200 new staff over the 3 year period (227, 562, and 387 in each fiscal year, respectively).[33] (See fig. 3.) Additionally, in fiscal year 2016 FDA hired 346 new staff to support the GDUFA program, although there was no associated GDUFA hiring goal for that fiscal year. The majority of these new hires support generic drug program evaluation activities within CDER, with additional hires distributed across other FDA offices.[34]

[33]According to FDA officials, the GDUFA hiring goal of 923 new staff was an estimate of the resources needed to eliminate the application backlog and review new incoming applications at the time of the GDUFA program negotiations in 2012. However, based upon ongoing assessments of the program's needs, FDA officials told us that the agency continued to hire new staff beyond the initial hiring goal in order to continue reducing the application backlog as well as to manage the influx of generic drug applications.

[34]FDA exceeded its overall generic drug program hiring goal as well as the fiscal year 2014 and 2015 goals, even after some new GDUFA hires left FDA or transferred to other FDA offices or centers.

Figure 3: FDA's Generic Drug User Fee Amendments of 2012 (GDUFA) Program Hiring Goals and Actual Hires, Fiscal Years 2013 through 2016



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-17-452

Notes: Figures in all bars reflect the total number of GDUFA new hires, including those that left FDA at any point from fiscal years 2013 through 2016. In fiscal year 2013, 1 new hire left FDA; in fiscal year 2014, 9 left FDA; in fiscal year 2015, 36 left FDA; and in fiscal year 2016, 48 left FDA.

Figures in all bars also include new hires that left their original position for another position within FDA at any point from fiscal years 2013 through 2016. In fiscal year 2013, this included 2 new hires; in fiscal year 2014, 20 new hires; in fiscal year 2015, 77 new hires; and in fiscal year 2016, 118 new hires. According to FDA officials, data are not available that identify whether the new positions involve generic drugs program work.

FDA did not have a GDUFA-related hiring goal in fiscal year 2016.

Information Technology

To fulfill its GDUFA commitments, FDA established a new Informatics Platform to improve the efficiency of application reviews and to support the agency's ability to track its performance. Prior to rolling out this platform in fiscal year 2015, FDA officials said that the agency used many disparate and disconnected databases, systems, and spreadsheets to manage different aspects of the generic drug review program. Officials said that the new platform integrates all these review functions, tracking the work flow from the time FDA receives an application until a decision is

made on it.[35] Furthermore, officials told us the platform can provide information on an application as it proceeds through the review process, and agency officials can also track when each assignment related to this process has been completed.[36] Backlog applications are also tracked by the platform.[37] During the initial launch, officials said that the platform was able to track the application review process and its related work flow, including analytics and metrics reporting. Since then, FDA has also incorporated data about facility inspection decisions as well as provided access to historical reviews and actions taken by FDA on generic drug applications submitted prior to fiscal year 2015. FDA officials said that the agency has plans to expand the use of the platform in the future to track additional incoming submissions, such as reports of drug shortages and applications for brand-name drugs. According to FDA officials, the launch of the platform has provided the following benefits to FDA and to stakeholders: (1) faster review times, (2) easier collaboration and communication with industry, (3) improved application review consistency, and (4) more predictable application review times and target completion dates due to having all pertinent information regarding an application in one location that is accessible to all FDA reviewers.

External Communication

As part of FDA's GDUFA commitments to streamline the review process, the agency took steps to change how it communicates with generic drug applicants. According to FDA officials, prior to GDUFA, deficiency letters were sent to applicants by specific types of reviewers within CDER—such as labeling reviewers or chemistry reviewers—in an uncoordinated fashion, making it difficult for applicants to obtain a comprehensive picture of their application's status. Starting in fiscal year 2013, FDA committed to consolidating all application deficiencies into one letter to the applicant, called a complete response letter. According to FDA officials, this systemic approach to provide a single deficiency letter was one of the

[35]FDA officials told us that the Informatics Platform consists of three complementary software components: (1) Integrity, which is an integrated data management system that ensures synchronization of data across CDER; (2) Panorama, which is a user interface component that allows FDA officials to manage, execute, track, and report on work commitments; and (3) Mercado, a component used to generate reports on FDA's metrics and conduct analyses on its progress toward meeting Commitment Letter goals.

[36]According to FDA officials, the platform can also be used by FDA to forecast future workload, perform capacity analyses, and track citizen petitions and congressional inquiries.

[37]Backlog applications refer to generic drug applications whose review status was pending as of October 1, 2012 (the date GDUFA went into effect).

biggest changes the agency made to the review process since the enactment of GDUFA.

Additionally, in September 2013, OGD issued guidance that established regulatory project managers as the central point of contact for each application throughout its lifecycle. FDA officials said that regulatory project managers are also responsible for overseeing the review of each application across all disciplines. Prior to GDUFA, FDA officials said that no one individual at the agency had responsibility for an application throughout its entire lifecycle.

FDA has also issued new and revised guidance documents to educate applicants about changes to the generic drug application review process made in response to GDUFA. According to FDA officials, since fiscal year 2013 FDA has issued 31 new and revised draft or final guidance documents related to the application review process. Additionally, officials said that FDA has also issued almost 600 new or revised product-specific recommendations to assist the applicants with identifying the most appropriate methodology for developing generic drugs and generating evidence needed to support application approval.[38]

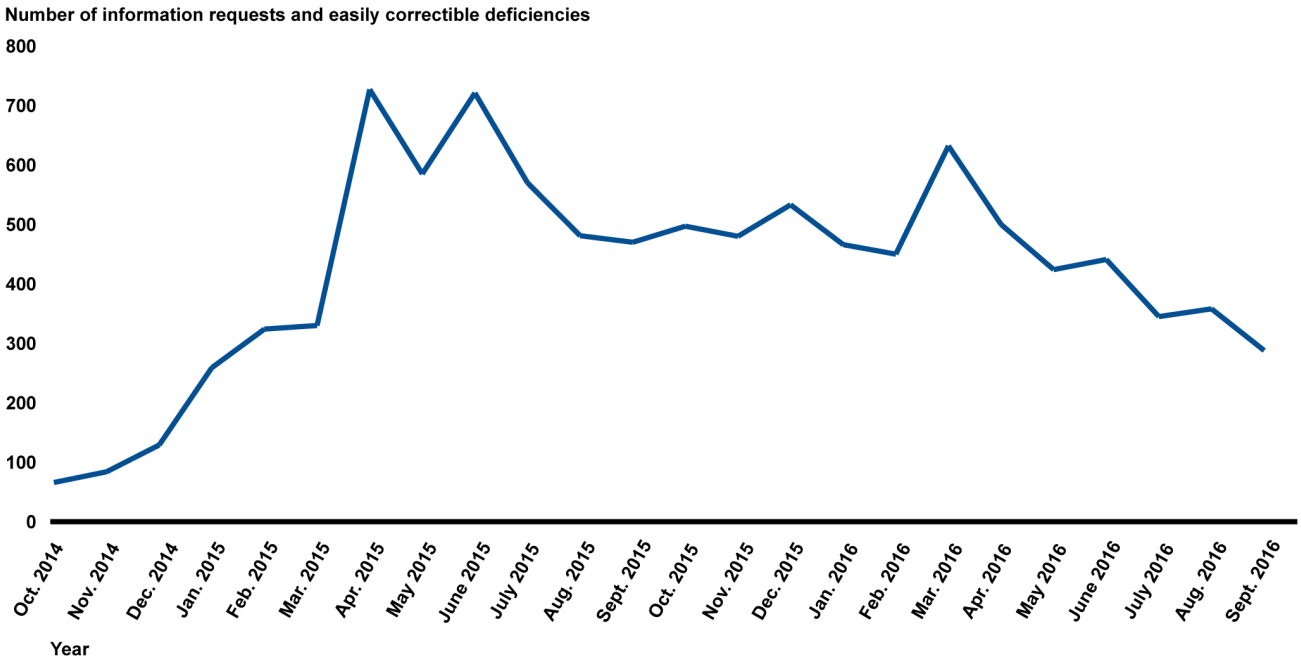
FDA Has Made Additional Refinements to Its Generic Drug Program in Response to Applicants' Concerns about Program Changes

FDA has made additional refinements to its application review program in response to applicant concerns about program changes. Specifically, to provide more timely communication on individual applications, FDA instituted a mechanism known as real time communication in late 2014. As described above, as one of its initial changes, FDA identified all deficiencies found in its review of an application in a single, complete response letter to the applicant. However, applicants told us that they found that only providing information in the complete response letters resulted in fewer informal communication opportunities with FDA and requested that FDA send information concerning individual application deficiencies on a rolling basis so that they could address deficiencies in real time. FDA acknowledged that the initial changes to how it communicated to applicants made it harder for applicants to assess the status of their applications and to plan the market launch of generic medicines. To remedy applicants' concerns and to enhance the review process by increasing transparency and decreasing the number of review

[38]FDA publishes product-specific recommendations describing the agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference drugs.

cycles, FDA implemented real-time communications—specifically "information requests" and "easily correctible deficiencies." According to FDA officials, information requests are used by application reviewers to informally notify applicants of any preliminary application concerns as well as to seek resolution and clarification on some of the minor issues related to the application. Similarly, application reviewers communicate easily correctible deficiencies to applicants to obtain missing information that should be readily available, to seek clarification of data already submitted, or to request final resolution of technical issues. FDA data show that the numbers of information requests and easily correctible deficiencies substantially increased in the first 9 months following their inception in early 2015 and have decreased somewhat since then, suggesting that both FDA and applicants have found these new forms of communication useful. (See fig. 4.)

Figure 4: Number of Information Requests and Easily Correctible Deficiencies Communications Issued by FDA for Abbreviated New Drug Applications, October 2014 through September 2016



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-17-452

FDA also revised its policy outlining the roles and responsibilities of various FDA staff in communicating with applicants during the application review process in August 2015. FDA made this revision to address stakeholder concerns that establishing regulatory project managers as

the primary point of contact for all communication with applicants limited the opportunities for informal communication with FDA staff directly responsible for reviewing applications. The revised policy expanded and set forth responsibilities and procedures for communications between FDA staff and applicants concerning the review status of applications. Specifically, OGD's regulatory project managers would remain responsible for communicating the review status of applications they manage, including transmitting complete response letters, while discipline project managers and Office of Pharmaceutical Quality regulatory business process managers—both of whom are more directly involved in an application's review—would be responsible for issuing all information requests and easily correctible deficiencies.[39] According to FDA officials, these changes were made as part of a broader effort to bring communications between the agency and applicants closer to "real-time."

Lastly, FDA has communicated target action dates to applicants since 2015 at the request of industry stakeholders. Target action dates are the agency's internal deadlines for taking action on generic drug applications pending with the agency on October 1, 2012, and those submitted in fiscal years 2013 and 2014 (years for which there were no GDUFA performance goals established). According to FDA, although GDUFA did not require the agency to establish and communicate target action dates to applicants, these dates help applicants plan product launches, which promotes timely access to generic drugs.

Generic Drug Application Review Times Have Decreased, with FDA Meeting Its GDUFA Performance Goals for Fiscal Year 2015

FDA's review times for generic drug applications have decreased since the implementation of GDUFA, with FDA surpassing multiple fiscal year 2015 GDUFA performance goals as described in table 4.

[39]According to FDA officials, discipline project managers facilitate an application's review within a specific discipline (e.g., bioequivalence or labeling); regulatory business process managers serve quality assurance functions and also coordinate internally to determine facility inspection status and provide that information to the designated review teams.

Table 4: Selected Generic Drug User Fee Performance Goals and Their Status, Fiscal Year 2015

Application type	Performance goal	Goal achieved
Abbreviated New Drug Applications (ANDA)[a]	Review and act on 60 percent of submissions within 15 months from the date of submission	Yes
Prior Approval Supplements (PAS)[b]		
Not requiring facility inspection	Review and act on 60 percent of PASs not requiring inspection within 6 months from the date of submission	Yes
Requiring facility inspection	Review and act on 60 percent of PASs requiring inspection within 10 months from the date of submission	Yes
Controlled correspondence[c]	Respond to 70 percent of controlled correspondence in 4 months from date of submission	Yes
Backlog[d]	Review and act on 90 percent of all ANDAs, ANDA amendments, and ANDA prior approval supplements regardless of current review status by 2017	Yes

Source: GAO analysis of Food and Drug Administration data. | GAO-17-452

[a]Generic drug applications are termed abbreviated by FDA because they are generally not required to include preclinical study data (studies involving animals) and clinical trial data (studies involving humans) to establish safety and effectiveness.

[b]An applicant must submit an application supplement to notify FDA of certain changes to its ANDA, such as changes to the manufacturing location or process, the type or source of active ingredients, or the labeling. If changes to the ANDA have a substantial potential to adversely affect factors such as the identity, quality, purity, or potency of the drug, the applicant must obtain FDA approval for the change through submission of a prior approval supplement.

[c]Controlled correspondence allows applicants to submit formal questions seeking the agency's input on issues capable of affecting the review of a product prior to their submission of an ANDA.

[d]Backlog applications refer to generic drug applications whose review status was pending as of October 1, 2012 (the date the Generic Drug User Fee Amendments of 2012 went into effect).

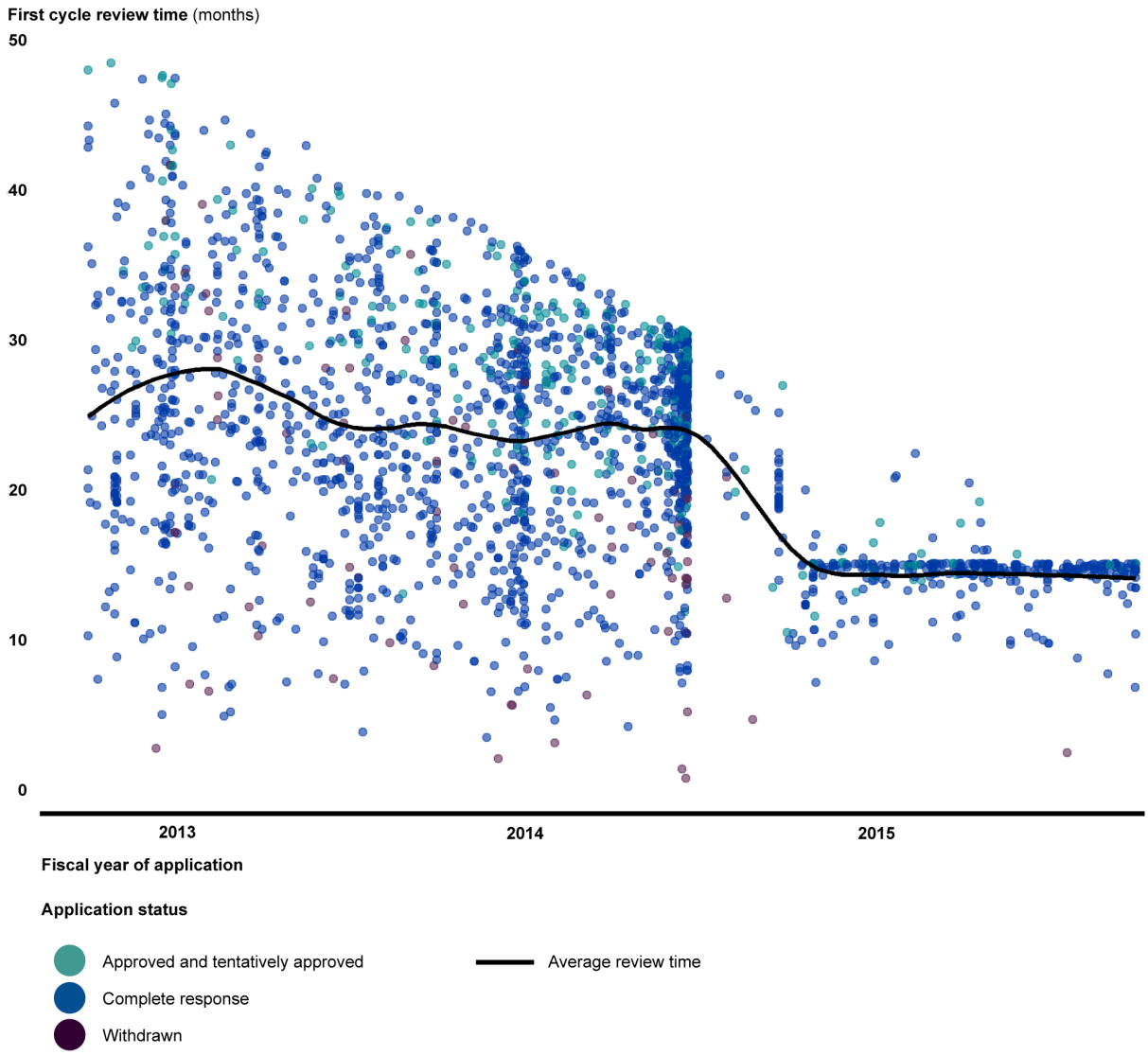
With respect to ANDA review times, the average time for FDA to complete the first review cycle decreased from 26 months for ANDAs submitted in fiscal year 2013 to about 14 months for those submitted in fiscal year 2015. Additionally, the dispersion in review times has decreased. (See fig. 5.) However, as of December 31, 2016, 929 ANDAs (34 percent) submitted since the start of the generic drug user fee program in fiscal year 2013 were still pending review. As these applications are reviewed, the average review time and the dispersion of review times for each fiscal year will increase since all of the applications

that remained to be acted on are at least 15 months old.[40] As of December 31, 2016, FDA had also acted on 89 percent of all ANDAs submitted in fiscal year 2015 within 15 months of receipt, exceeding its GDUFA goal of acting on 60 percent of ANDAs received in fiscal year 2015 within 15 months.[41]

[40]As of December 31, 2016, 29 percent of ANDAs submitted in fiscal year 2013, 40 percent of ANDAs submitted in fiscal year 2014, and 26 percent of ANDAS submitted in fiscal year 2015 are still awaiting a first review.

[41]As of December 31, 2016, 81 percent of ANDAs submitted in fiscal year 2013, 62 percent of ANDAs submitted in fiscal year 2014, and 85 percent of ANDAs submitted in fiscal year 2015 received a complete response at the end of their first review cycle. In its fiscal year 2016 GDUFA Performance Report, FDA reported that 98 percent of completed actions on ANDAs had met the review-time goal and that, once all pending reviews are completed, a minimum of 79 percent and a maximum of 98 percent of ANDAs would meet the goal. Food and Drug Administration, *FY 2016 Performance Report to Congress for the Generic Drug User Fee Amendments* (Silver Spring, Md.: 2016). While we did not include applications that received a refuse to receive letter in our analyses of completed applications, these applications with refuse to receive letters count toward FDA meeting its GDUFA goal. The percent of ANDAs meeting the GDUFA goal would have increased if we had included these applications.

Figure 5: Decrease in FDA First Cycle Review Time for Abbreviated New Drug Applications, Fiscal Years 2013 through 2015

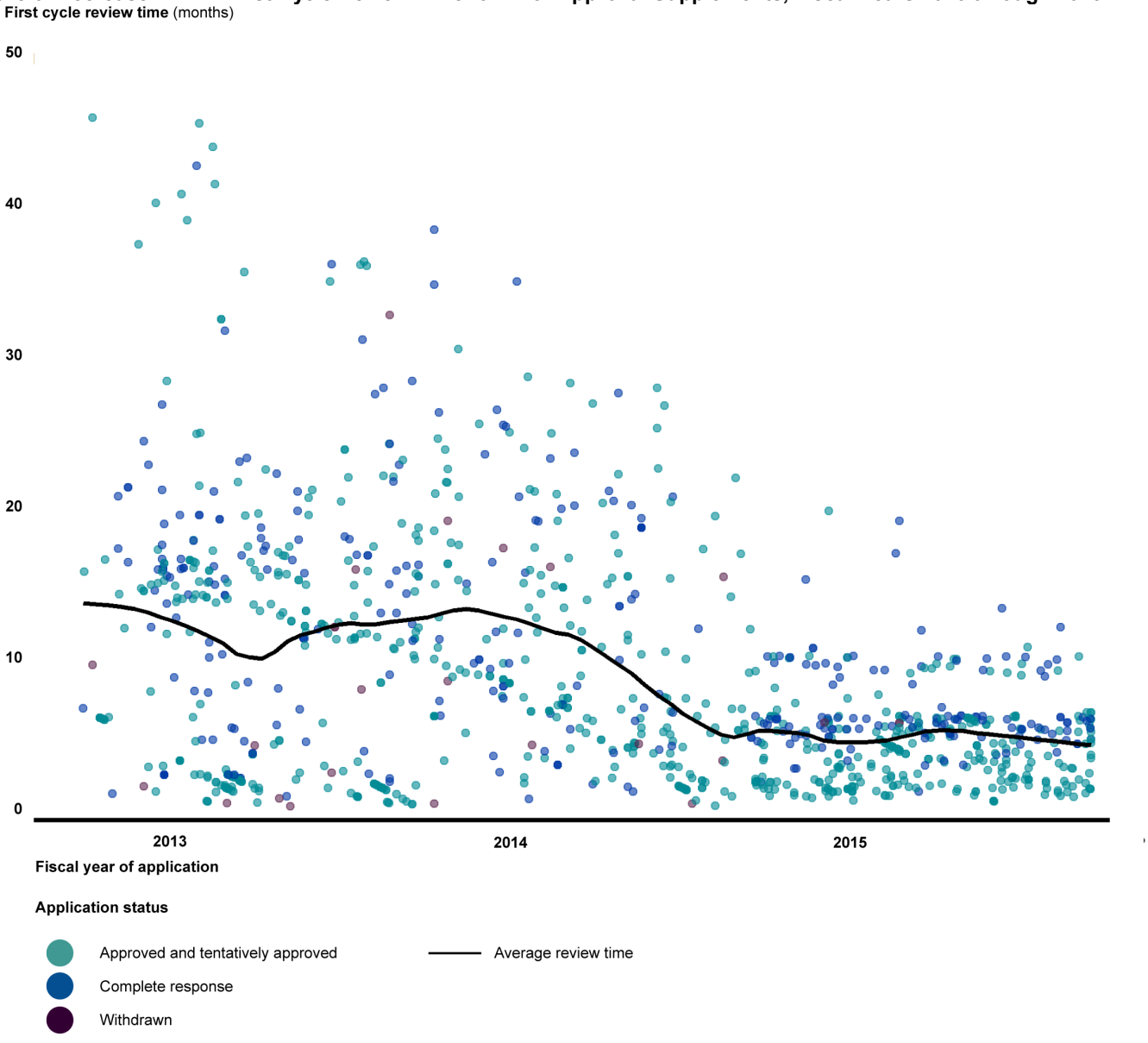


Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-17-452

Note: Approved: FDA issues an approval letter to an applicant when the agency has concluded its review of a generic drug application and the applicant is authorized to commercially market the drug. Tentatively approved: FDA issues a tentative approval letter when the agency has completed its review of an application, but patents or other exclusivities granted to the original, brand-name product prevent approval. A tentative approval letter does not allow the applicant to market the generic drug product until the related patents and other exclusivities no longer prevent approval. Complete response: FDA issues a complete response letter to an applicant at the completion of a full application review where deficiencies are found—the complete response letter describes any deficiencies that must be corrected in order for an application to be approved.

For PASs, the average time for FDA to complete the first review cycle also declined from 12 months in fiscal year 2013 to 4.5 months in fiscal year 2015. Additionally, the dispersion in review times decreased, as shown in figure 6.

Figure 6: Decrease in FDA First Cycle Review Time for Prior Approval Supplements, Fiscal Years 2013 through 2015



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-17-452

Note: Approved: FDA issues an approval letter to an applicant when the agency has concluded its review of a generic drug application and the applicant is authorized to commercially market the drug. Tentatively approved: FDA issues a tentative approval letter when the agency has completed its review of an application, but patents or other exclusivities granted to the original, brand-name product prevent approval. A tentative approval letter does not allow the applicant to market the generic drug product until the related patents and other exclusivities no longer prevent approval. Complete response: FDA issues a complete response letter to an applicant at the completion of a full application review where deficiencies are found—the complete response letter describes any deficiencies that must be corrected in order for an application to be approved.

FDA acted within 6 months on 95 percent of the PASs it received in fiscal year 2015 not requiring a facility inspection, exceeding its GDUFA goal of acting on 60 percent of PASs received within 6 months of receipt. For PASs received in fiscal year 2015 that required a facility inspection, FDA acted on 92 percent within 10 months, again exceeding its GDUFA goal of acting on 60 percent within 10 months of receipt.[42]

FDA has also met performance goals related to controlled correspondences and its review of backlogged applications. As of December 31, 2016, FDA acted on 97 percent of the 1,519 controlled correspondences it received in fiscal year 2015 within 4 months, exceeding its GDUFA goal of acting on 70 percent within 4 months of receipt. FDA was unable to provide more detailed information on the review times for controlled correspondences submitted in the first 2 years of the program; however, according to FDA officials, 2,027 of the 2,040 correspondences submitted in that period have been reviewed as of August 2016.

In addition, as of December 31, 2016, FDA had acted on 92 percent of the 4,743 applications in the backlog pending review as of October 1, 2012, exceeding its GDUFA goal of acting on 90 percent of such applications before the end of fiscal year 2017. Fifty-eight percent of these applications were approved; approximately 20 percent were withdrawn by the applicant; and the applicants for the remaining 12 percent received a complete response letter.

Conclusions

As with any appropriations, the user fee funding provided to FDA brings with it a great responsibility to manage funds in a way that demonstrates prudent stewardship of resources. FDA has used its user fee funding to enhance OGD's ability to increase hiring, and undertake numerous activities to improve and speed-up the review of generic drug applications. However, at the end of each fiscal year FDA has had large

[42]As of December 31, 2016, 64 percent of PASs submitted in fiscal year 2013, 69 percent of PASs submitted in fiscal year 2014, and 70 percent of PASs submitted in fiscal year 2015 were approved in their first review cycle; 30 percent of PASs submitted in fiscal year 2013, 22 percent of PASs submitted in fiscal year 2014, and 28 percent submitted in fiscal year 2015 received a complete response. While we did not include applications that received a refuse to receive letter in our analyses of completed applications, these applications with refuse to receive letters count toward FDA meeting its GDUFA goal. The percent of PASs meeting the GDUFA goal would have increased if we had included these applications.

GDUFA carryover balances, and FDA has not fully documented the underlying assumptions for the size of the carryover, including anticipated obligations. Such a documented plan could aid Congress in determining the appropriate amount of user fees to be collected by the agency during the annual appropriations process and when considering a reauthorization of the user fee program. Making this information publicly available would also help to ensure that FDA's recommendations to Congress are fully informed by the views of external stakeholders with whom FDA has an obligation to consult.

Recommendation for Executive Action

To ensure efficient use of generic drug user fees, facilitate oversight and transparency, and plan for risks, we recommend that the Commissioner of FDA develop a plan for administering user fee carryover that includes analyses of program costs and risks and reflects actual operational needs and contingencies.

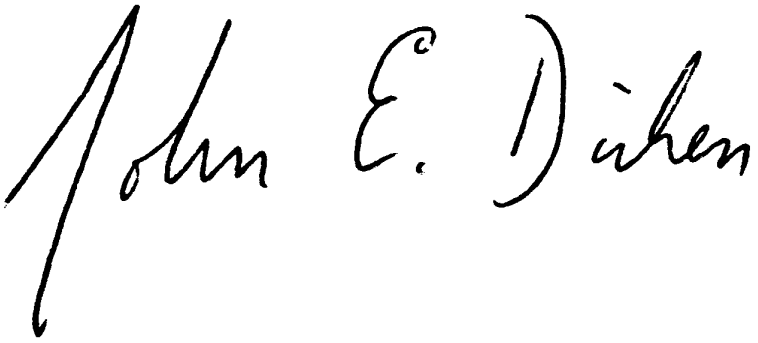
Agency Comments

We provided a draft of this report to HHS for comment. In its written comments, which are reproduced in appendix II, HHS concurred with our recommendation. HHS agreed that it should incorporate an analysis of program risks and contingencies into its existing 5-year financial planning process and that it will review appropriate actions. HHS also provided technical comments, which we incorporated as appropriate.

As agreed with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the appropriate congressional committees, the Secretary of HHS, 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 John E. Dicken at (202) 512-7114 or DickenJ@gao.gov. Contact points for our Office of Congressional Relations and Office of Public Affairs can be found on the last page of this report. Other major contributors to this report are listed in appendix III.

Sincerely yours,



John E. Dicken
Director, Health Care

Appendix I: Regulatory Science Projects Supported by Generic Drug User Fees, Fiscal Years 2013 through 2016

Regulatory science projects support the development of generic drugs in part by helping to address gaps the agency faces between rapid changes in science and technology and the agency's capacity to regulate those technologies.[1] We previously reported that the Food and Drug Administration (FDA) traditionally funds regulatory science projects with resources from the agency's regular appropriations, but projects funded within the Center for Drug Evaluation and Research (CDER) have also been supplemented by funds collected from user fee acts, such as the Prescription Drug User Fee Act and the Generic Drug User Fee Amendments of 2012 (GDUFA).[2] GDUFA funds accounted for approximately $20 million in annual obligations for regulatory science projects from fiscal years 2013 through 2016.

The Office of Generic Drugs (OGD), located within CDER, established the GDUFA Regulatory Science Research Program to support projects that could potentially enhance the development of generic drugs. In fiscal year 2013, OGD created a list of GDUFA Regulatory Science Priorities that includes five broad priority areas (see table 5). The list is based in part on discussions with stakeholders during annual public meetings on GDUFA and in part on stakeholder comments to FDA's GDUFA regulatory science funding announcements.[3] However, generic drug industry stakeholders have raised concerns about the need for more meaningful scientific dialogue about FDA's requirements for the development of generic drugs, and for more clarity on how the agency develops its regulatory science priorities list. FDA officials we interviewed were cognizant of stakeholders' concerns and noted that they have

[1]The Food and Drug Administration (FDA) defines regulatory science as the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated projects. See GAO, *Medical Product Oversight: FDA Needs More Strategic Planning to Guide Its Scientific Initiatives.* GAO-16-432 (Washington, D.C.: May 16, 2016). See also GAO, *High-Risk* Series: An Update, GAO-13-283 (Washington, D.C.: February 2013); *Prescription Drugs: FDA Has Met Most Performance Goals for Reviewing Applications*, GAO-12-500 (Washington, D.C.: Mar. 30, 2012); and *Drug Shortages: FDA's Ability to Respond Should be Strengthened*, GAO-12-116 (Washington, D.C.: Nov. 21, 2011).

[2]GAO-16-432.

[3]The Commitment Letter provides that FDA will convene a working group to develop an annual list of regulatory science activities specific to generic drugs. FDA is to hold public hearings to provide an overview of the status of regulatory science initiatives for generic drugs and an opportunity for public input on research priorities to enhance the development of generic drugs. FDA awards grants and contracts to researchers to pursue research relating to these initiatives.

reconsidered the five broad categories each year. However, officials told us they have not made changes to the priority areas since they were established in fiscal year 2013 and do not envision annual changes to the broad categories, though the sub-priority areas in each category have been revised from year to year. The officials acknowledged that while some information about their process for judging the merit of regulatory science proposals is public, details about how proposals are scored is not public in order to promote a process whereby applications submitted are evaluated free of bias from stakeholders. The officials explained that the priorities list is created internally at FDA in part to protect the privacy of applicants that submitted proposals, to avoid potential conflicts of interest from stakeholders who may want to steer research away from competitors, and to incorporate internal FDA capabilities to conduct research at lower costs. Although the officials said that decisions about which projects to fund is an inherently governmental function and should be made internally to support public health, they noted plans to improve communications with industry about the priorities list and plan to more clearly announce the sub-priority areas available for research on the OGD webpage.

Table 5: Regulatory Science Priorities to Enhance the Development of Generic Drugs, Supported by Generic Drug User Fees, Fiscal Years 2014 through 2016

User fee priority areas	Description
Post-market evaluation of generic drugs	Includes research into monitoring methods, understanding patient perceptions of generic drug quality and effectiveness, and verifying therapeutic equivalence via patient brand-to-generic switching studies.
Equivalence of complex drug products	Includes research into making generic versions available in all product categories, including complex drugs with unique characteristics.
Equivalence of locally acting products	Includes research into new bioequivalence methods and pathways for locally-acting drugs.
Therapeutic equivalence evaluation and standards	Includes research that supports the evolution of risk-based equivalence and product quality standards to ensure therapeutic equivalence across all dosage forms and routes of delivery.
Cross-cutting computational and analytical tools	Includes developments and research that impact the other four GDUFA regulatory science priority areas and are essential to modernizing the abbreviated new drug application review process.

Source: GAO analysis of Food and Drug Administration data. | GAO-17-452

In the first 4 years following GDUFA's implementation, OGD obligated a cumulative amount of about $77 million from generic drug user fee collections for 103 regulatory science projects. Data provided by FDA showed that 15 of these projects supported research into post-market evaluation of generic drugs, 30 projects supported the equivalence of complex drug products, 20 projects supported the equivalence of locally acting products, 20 supported therapeutic equivalence evaluation and standards, and 18 supported cross-cutting computational and analytical tools. Obligations from user fees for regulatory science projects remained relatively stable each year, from a low of $16 million in fiscal year 2016 to a high of $24 million in fiscal year 2015.[4] (See table 6). According to FDA officials, the agency is not required by law or otherwise committed to spend a certain amount on regulatory science projects, but agency officials anticipate funding projects at similar levels in future years.

Table 6: Generic Drug User Fee-Funded Regulatory Science Research Projects, by Priority Area, Fiscal Years (FY) 2013 through 2016

		Dollars				
Grant or contract name[a]	**User fee priority area**	**FY 2013**	**FY 2014**	**FY 2015**	**FY 2016**	**Total user fees obligated**
Development of bio-relevant in-vitro assay to determine labile iron in the parenteral iron complex product	2	499,999	0	0	0	**499,999**
An IVIVIC system to facilitate the development of a generic vitrasert	2	499,280	0	0	0	**499,280**
Development of an in vitro dissolution technique to understand the clinical based outcomes of orally inhaled drug particles	3	200,000	44,999	0	49,977	**294,976**
Assessing clinical equivalence for generic drugs approved by innovative methods	1	247,696	0	0	0	**247,696**
Clinical practice data to aid narrow therapeutic index drug classification	4	247,024	249,895	0	0	**496,919**
An optimized dissolution test system for orally inhaled drugs: development and validation	3	199,961	45,000	11,249	0	**256,210**

[4]Some regulatory science projects spanned multiple fiscal years and received funding in more than one year.

		Dollars				
Grant or contract name[a]	User fee priority area	FY 2013	FY 2014	FY 2015	FY 2016	Total user fees obligated
Comprehensive evaluation of formulation effects on metered dose inhaler performance	3	700,000	300,000	0	0	**1,000,000**
Therapeutic index evaluation for Tacrolimus and Levetiracetam	4	205,621	0	0	0	**205,621**
Novel methodologies and in vitro in vivo correlation approaches to assess bioequivalent of topical drugs	3	500,000	250,000	0	0	**750,000**
In vitro in vivo correlations of ocular implants	2	565,405	0	0	0	**565,405**
Tiered testing strategy for assessing thermal effects on transdermal products	2	494,430	249,995	250,000	0	**994,425**
In vitro in vivo correlations of parenteral microsphere drug products	2	489,557	499,994	124,999	0	**1,114,550**
Evaluation of dissolution methods for complex parenteral liposomal formulations	2	402,157	0	0	0	**402,157**
Bioequivalence of topical drug products: In vitro in vivo correlations	2	499,999	499,998.00	499,999	350,000	**1,349,998**
Heat effect on generic transdermal drug delivery systems	2	500,000	700,000	499,999	499,998	**2,199,997**
Postmarketing surveillance of generic drug usage and substitution patterns	1	250,000	250,000	0	0	**500,000**
In vitro in vivo correlations of parenteral microsphere drug products	2	500,000	0	125,000	0	**625,000**
In vitro fluid capacity-limited dissolution testing and its kinetic relation to in vivo clinical pharmacokinetics for orally inhaled drug products	3	199,995	45,000	11,229	49,997	**306,221**
Bioequivalence and clinical implications of generic bupropion	1	800,000	1,000,000	1,000,000	0	**2,800,000**
Development of a liposome doxorubicin product drug release assay	2	467,811	249,996	0	0	**717,807**
Variation in the physical characteristics of generic drugs affecting patient experiences: survey of pharmacists and patients	4	749,892	583,264	0	0	**1,333,156**

		Dollars				
Grant or contract name[a]	User fee priority area	FY 2013	FY 2014	FY 2015	FY 2016	Total user fees obligated
Effect of different protective packaging configurations on stability of fluticasone propionate capsules for inhalation	3	199,992	0	0	0	**199,992**
Investigate the sensitivity of pharmacokinetics in detecting differences in physicochemical properties of the active in suspension nasal products for local action	3	1,418,088	0	43,813	0	**1,461,901**
Evaluation of drug product formulation and in-vitro performance characteristics related to abuse-deterrence for solid oral dosage forms of opioids	4	499,000	0	0	0	**499,000**
Evaluation of clinical and safety outcomes associated with conversion from brand-name to generic tacrolimus products in high risk transplant recipients	1	2,250,981	0	0	0	**2,250,981**
Correlation of mesalamine pharmacokinetics with local availability	3	500,000	0	0	0	**500,000**
Investigation of inequivalence of bupropion hydrochloride extended release tablets: in vitro metabolism quantification	1	100,000	120,000	0	0	**220,000**
Pharmacokinetic study of bupropion hydrochloride products with different release patterns	1	1,300,659	0	0	0	**1,300,659**
Prediction of in vivo performance for oral solid dosage forms	4	2,206,535	1,320,250	1,679,000	0	**5,205,785**
Development of hydrogel-based in vitro dissolution apparatus for microparticle formulations	2	0	125,625	155,469	22,298	**303,392**
Development of hybrid CFD-PBPK models for absorption of intranasal corticosteroids	5	0	200,000	200,000	199,948	**599,948**
Transplant outcomes using generic and brand name immune-suppressants: medications used for kidney and liver transplants	1	0	494,072	471,900	0	**965,972**
Physiologically based pharmacokinetic model for drugs encapsulated into liposomes	5	0	198,529	175,978	264,064	**638,571**

		Dollars				
Grant or contract name[a]	User fee priority area	FY 2013	FY 2014	FY 2015	FY 2016	Total user fees obligated
Assessing the post-marketing safety of authorized generic drug products	1	0	185,611	185,595	0	**371,206**
A predictive multiscale computational tool for simulation of lung absorption and pharmacokinetics and optimization of pulmonary drug delivery	5	0	148,122	149,397	150,196	**447,715**
An integrated multiscale-multiphysics modeling and simulation of ocular drug delivery with whole-body pharmacokinetic response	5	0	148,482	151,132	154,169	**453,783**
Topical ophthalmic suspensions: new methods for bioequivalence assessment	3	0	249,880	53,063	0	**302,943**
A model and system based approach to efficacy and safety questions related to generic substitution	5	0	249,999	249,999	249,999	**749,997**
Pharmacokinetic and pharmacodynamic studies of cardiovascular drugs	1	0	622,350	981,267	729,254	**2,332,871**
Effect of therapeutic class on generic drug substitutions	1	0	220,213	220,213	0	**440,426**
Pharmacokinetic pharmacodynamic studies of methylphenidate extended release products in pediatric attention deficit hyperactivity disorder	1	0	1,000,010	1,000,000	1,249,480	**3,249,490**
Integrated approach to determine equivalence in complex drug mixtures	5	0	600,000	0	0	**600,000**
Formulation, processing and performance interrelationship for amorphous solid dispersions	4	0	500,000	500,000	500,000	**1,500,000**
Characterization of critical quality attributes for semisolid topical drug products	3	0	249,750	249,750	250,000	**749,500**
Physiologically based biopharmaceutics and pharmacokinetics of drug products for dermal absorption in humans	5	0	200,000	200,000	200,000	**600,000**

		Dollars				
Grant or contract name[a]	User fee priority area	FY 2013	FY 2014	FY 2015	FY 2016	Total user fees obligated
Development and validation of dermal PBPK modeling platform toward virtual bioequivalence assessment considering population variability	5	0	126,114	130,445	134,950	**391,509**
Physiologically based pharmacokinetic modeling and simulation for ocular dosage forms	5	0	201,916	200,000	200,000	**601,916**
Dissolution methods for topical ocular emulsions	3	0	250,000	62,492	0	**312,492**
Prospective study comparing brand and generic immunosuppression on transplant outcomes adherence and immune responses	1	0	1,000,000	1,413,028	0	**2,413,028**
Dissolution methods for parenteral sustained release implant drug products	2	0	250,000	206,486	51,508	**507,994**
Dissolution methods for predicting bioequivalence of ocular semi-solid formulations	3	0	348,705	87,175	0	**435,880**
Evaluation and development of dissolution testing methods for semisolid ocular drug products	3	0	349,885	87,464	0	**437,349**
Modeling of the vitreous for in vitro prediction of drug delivery of porous silicon particles and episcleral plaques	2	0	267,721	232,279	0	**500,000**
Evaluation of iron species in healthy subjects treated with generic and reference sodium ferric gluconate	1	0	500,000	500,000	711,400	**1,711,400**
Population pharmacokinetic and pharmacodynamic, dose-toxicity modeling and simulation for narrow therapeutic index (NTI) drugs	5	0	207,980	196,098	201,706	**605,784**
Pharmacometic modeling and simulation for generic drug substitutability evaluation and post marketing risk assessment	5	0	207,980	196,098	201,705	**605,783**
Topical products and critical quality attributes	3	0	250,000	270,000	250,000	**770,000**
Pharmacometric modeling of immunosuppressants for evaluation of bio-equivalence criteria	5	0	250,000	250,000	250,000	**750,000**

		Dollars				
Grant or contract name[a]	User fee priority area	FY 2013	FY 2014	FY 2015	FY 2016	Total user fees obligated
Development of clinically relevant in vitro performance test for generic orally inhaled drug products: Physiological models for aerodynamic particle size distribution analysis	3	0	254,864	234,433	93,727	**583,024**
Evaluation of in vitro release methods for Liposomal Amphotericin B	2	0	499,983	0	0	**499,983**
Characterization of epilepsy patients at-risk for adverse outcomes related to switching antiepileptic drug products	4	0	1,539,798	0	0	**1,539,798**
Bioequivalence study of lamotrigine extended tablets in healthy subjects	4	0	1,198,687	291,366	30,500	**1,520,553**
Educating groups influencing generic drug use	1	0	0	249,990	249,853	**499,843**
Novel approaches for confounding control in observational studies of generic drugs	5	0	0	200,000	197,852	**397,852**
Identifying messages to promote value and education of generic prescribing	1	0	0	250,000	250,000	**500,000**
Comprehensive evaluation of formulation effects on metered dose inhaler performance	3	0	0	463,695	200,000	**663,695**
A model and system based approach to efficacy and safety questions related to generic substitution	5	0	0	249,999	249,999	**499,998**
Structural nested models for assessing the safety and effectiveness of generic drugs	5	0	0	199,999	199,999	**399,998**
Bio-relevant dissolution methods for particulate dosage forms in the periodontal pocket	2	0	0	125,000	174,727	**299,727**
Development of physiologically based pharmacokinetic simulation for long-acting injectable microspheres	2	0	0	200,000	200,000	**400,000**
Development of a dissolution method for long-acting periodontal drug products	2	0	0	125,000	125,000	**250,000**

		Dollars				
Grant or contract name[a]	User fee priority area	FY 2013	FY 2014	FY 2015	FY 2016	Total user fees obligated
Development of real-time and accelerated dissolution methods for a long-acting Levonorgestrel intrauterine system	2	0	0	170,000	125,000	**295,000**
Prediction and testing of excipient molecular targets	4	0	0	410,966	0	**410,966**
Interactions of excipients with intestinal transporters	4	0	0	383,609	0	**383,609**
Prediction and testing of excipient molecular targets	4	0	0	0	400,000	**400,000**
Interactions of excipients with intestinal transporters	4	0	0	0	400,000	**400,000**
Data-fusion based platform development of population PKPD modeling and statistical analysis for bioequivalence assessment of long-acting injectable products	2	0	0	199,983	199,945	**399,928**
Pharmacometric modeling and simulation for evaluation of bioequivalence for leuprolide acetate injection	2	0	0	200,000	200,000	**400,000**
Evaluation of the ex vivo release profile of a long-acting biodegradable periodontal dosage form in a canine periodontal disease model	2	0	0	214,300	0	**214,300**
Comparative surveillance of generic drugs by machine learning	5	0	0	630,208	0	**630,208**
Computational drug delivery; leveraging predictive models to develop bioequivalent generic long-acting injections	2	0	0	290,940	0	**290,940**
In vivo predictive dissolution to advance oral product bioequivalence regulation	4	0	0	1,248,178	0	**1,248,178**
Influence of raw materials, manufacturing variables, and storage conditions on release performance of long acting release microsphere products	2	0	0	1,000,000	0	**1,000,000**

		Dollars				
Grant or contract name[a]	User fee priority area	FY 2013	FY 2014	FY 2015	FY 2016	Total user fees obligated
Wireless sampling pill to measure in vivo drug dissolution in gastro-intestinal tract and computational model to distinguish meaningful product quality differences and ensure bioequivalence in patients	4	0	0	2,100,000	0	**2,100,000**
Bioequivalence of generic methylphenidate	4	0	0	943,521	49,136	**992,657**
Pharmacokinetics study of opioid drug product following insufflation of milled drug products	4	0	0	922,804	0	**922,804**
Novel method to evaluate bioequivalence of nanomedicines[b]	2	0	0	0	400,000	**400,000**
Generic drug substitution in special populations	4	0	0	0	199,998	**199,998**
Enhancing the reliability, efficiency, and usability of Bayesian population modeling	5	0	0	0	250,000	**250,000**
A cluster-based assessment of drug delivery in asthmatic small airways	3	0	0	0	199,996	**199,996**
Development of a universal bioequivalence test method for topical drugs	3	0	0	0	500,000	**500,000**
Benchmark of dermis microdialysis to assess bioequivalence of dermatological topical products	3	0	0	0	250,000	**250,000**
Design, development, implementation and validation of a mechanistic physiologically-based pharmacokinetic framework for the prediction of the in vivo behavior of supersaturating drug products	4	0	0	0	250,000	**250,000**
Investigation of peptide interactions in microsphere drug products	2	0	0	0	250,000	**250,000**
Advanced analytical techniques for mixed polymer drug-delivery systems	2	0	0	0	375,398	**375,398**
Mass spectrometry profiling of pentosan polysulfate in urine	2	0	0	0	223,057	**223,057**
Base IDIQ for postmarket bioequivalence study	4	0	0	0	2,500	**2,500**

		Dollars				
Grant or contract name[a]	**User fee priority area**	**FY 2013**	**FY 2014**	**FY 2015**	**FY 2016**	**Total user fees obligated**
Evaluation of formulation dependence of drug-drug interaction with proton pump inhibitors for oral extended-release drug products	4	0	0	0	999,243	**999,243**
Pharmacokinetic comparison of locally acting inhaled drug products	3	0	0	0	729,304	**729,304**
Critical process parameters for the preparation of Amphotericin B liposomes	2	0	0	0	497,310	**497,310**
Evaluation of model-based bioequivalence statistical approaches for sparse design PK studies	5	0	0	0	198,283	**198,283**
Pulsatile microdialysis for in vitro release of ophthalmic emulsions	2	0	0	0	236,500	**236,500**
Assessment of the in vitro percutaneous absorption, in vitro rate of release, and physicochemical properties of selected commercially available AT rated ointment formulations	2	0	0	0	$597,340	**597,340**
Totals		**17,694,083**	**19,004,669**	**24,324,607**	**16,425,316**	**77,448,674**

Legend:

User fee priority area 1 = Post-market evaluation of generic drugs

User fee priority area 2 = Equivalence of complex drug products

User fee priority area 3 = Equivalence of locally acting products

User fee priority area 4 = Therapeutic equivalence evaluation and standards

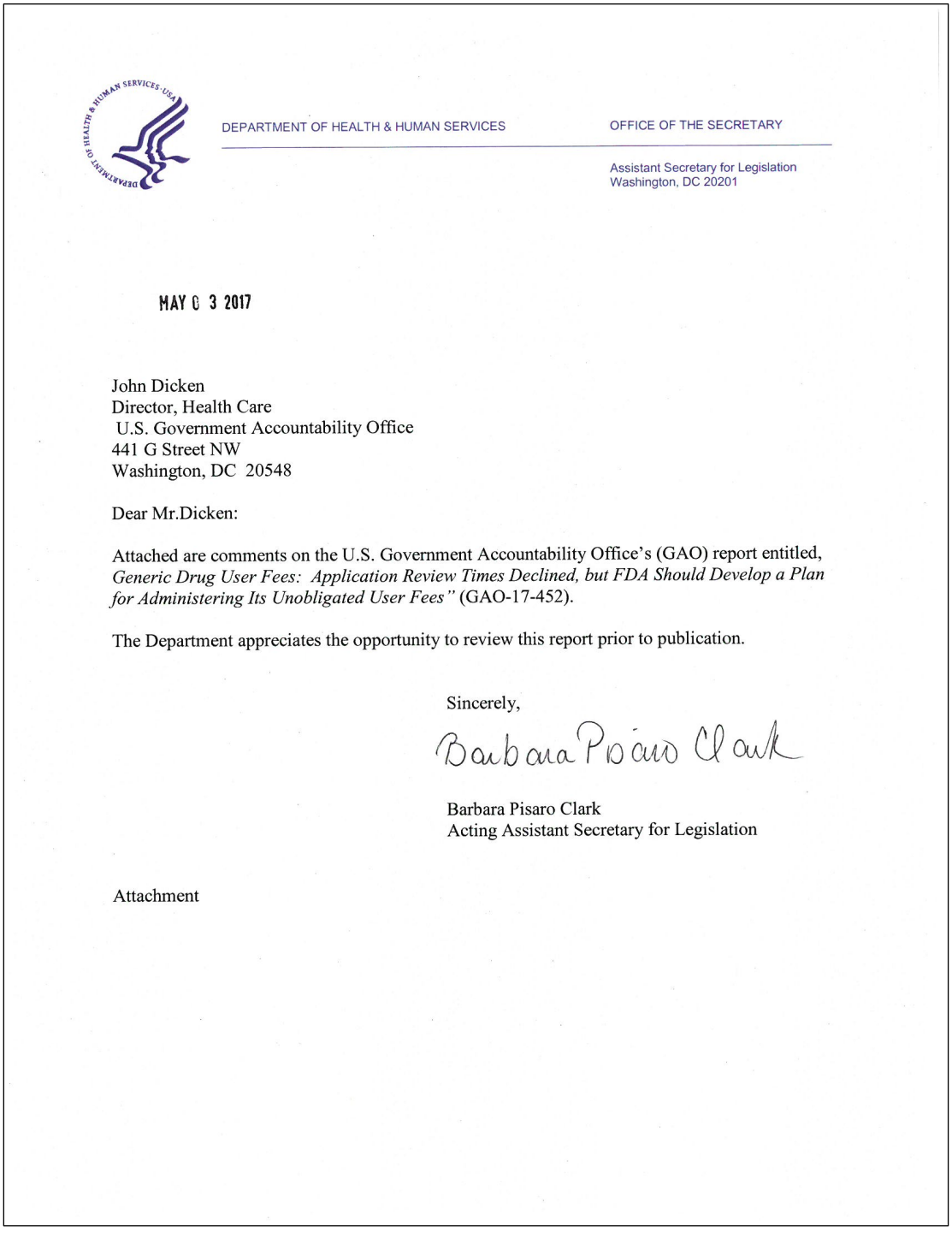
User fee priority area 5 = Cross-cutting computational and analytical tools

Source: GAO analysis of Food and Drug Administration data. | GAO-17-452

[a]The information presented in this column was obtained directly from FDA. We did not edit grant or contract names to correct typographical or grammatical errors, and we reprinted the abbreviations and acronyms as they were provided by FDA.

[b]In FY 2016, FDA funded an interagency agreement to support research on the equivalence of complex drug products.

Appendix II: 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

MAY 0 3 2017

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

Dear Mr.Dicken:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, *Generic Drug User Fees: Application Review Times Declined, but FDA Should Develop a Plan for Administering Its Unobligated User Fees"* (GAO-17-452).

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

Sincerely,

Barbara Pisaro Clark

Barbara Pisaro Clark
Acting Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: GENERIC DRUG USER FEES: APPLICATION REVIEW TIMES DECLINED, BUT FDA SHOULD DEVELOP A PLAN FOR ADMINISTERING ITS UNOBLIGATED USER FEES (GAO-17-452)

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

Recommendation

To ensure efficient use of generic drug user fees, facilitate oversight and transparency, and plan for risks, we recommend that the Commissioner of the Food and Drug Administration develop a plan for administering user fee carryover that includes analyses of program costs and risks and reflects actual operational needs and contingencies.

HHS Response

HHS concurs with GAO's recommendation. HHS agrees that it should incorporate an analysis of program risks and contingencies into its existing five-year financial planning process and will review appropriate actions.

Appendix III: GAO Contact and Staff Acknowledgments

GAO Contact

John E. Dicken, (202) 512-7114 or dickenj@gao.gov.

Staff Acknowledgments

In addition to the contact named above, individuals making key contributions to this report include Robert Copeland (Assistant Director); Carolina Morgan (Analyst-in-Charge); Enyinnaya David Aja; Nick Bartine; Taylor Dunn; Sandra George; Laurie Pachter; and Said Sariolghalam. Muriel Brown and Laurel Plume also made contributions to this report.