



August 2019

GENERIC DRUG APPLICATIONS

FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle

Accessible Version

GAO Highlights

Highlights of [GAO-19-565](#), a report to congressional committees

Why GAO Did This Study

Generic drugs—copies of brand-name drugs—lead to significant cost savings. Before a generic drug can be marketed, FDA must approve the generic drug application. According to FDA, applications go through an average of three cycles of review before being approved, which may take years.

The FDA Reauthorization Act of 2017 included a provision for GAO to study issues regarding the approval of generic drug applications in the first review cycle. This report examines 1) the first review cycle approval rate of generic drug applications in recent years and factors that may have contributed to whether applications were approved; and 2) changes FDA has made to increase the first review cycle approval rate. GAO reviewed FDA data on all generic drug applications reviewed from fiscal years 2015 through 2017 and documentation from the first review cycle for a judgmental selection of 35 applications from fiscal years 2017 and 2018. GAO also interviewed a non-generalizable selection of stakeholders. Applications and stakeholders were chosen to ensure variation in experience with the approval process.

What GAO Recommends

GAO recommends that FDA 1) take additional steps to address inconsistency in its written comments to generic drug application sponsors and 2) assess the extent to which the timing of brand-name drug companies' drug labeling changes affects the approval of generic drugs and take steps, as appropriate, to limit the effect. HHS concurred with GAO's recommendations.

View [GAO-19-565](#). For more information, contact John Dicken at (202) 512-7114 or dickenj@gao.gov.

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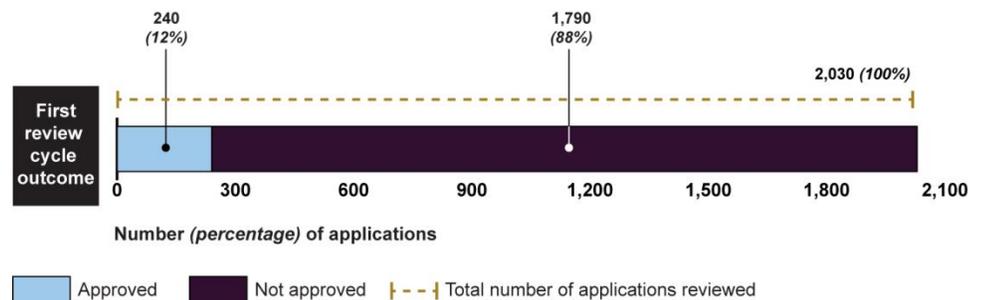
GENERIC DRUG APPLICATIONS

FDA Should Take Additional Steps to Address Factors That May Affect Approval Rates in the First Review Cycle

What GAO Found

GAO found that 12 percent of the 2,030 generic drug applications reviewed by the Food and Drug Administration (FDA) from fiscal years 2015 through 2017 were approved in the first review cycle. The first review cycle begins when FDA accepts a generic drug application for review and ends when FDA makes its first decision about whether the drug should be approved for marketing and sale. For applications that were not approved in that first cycle, the application must undergo one or more subsequent review cycles to obtain approval, delaying the generic drug's arrival to market.

Number and Percentage of Generic Drug Applications Approved in the First Review Cycle, Fiscal Years 2015–2017



Source: GAO analysis of Food and Drug Administration data. | GAO-19-565

GAO identified several factors that may have contributed to whether a generic drug was approved during the first review cycle. For example, certain types of complex drugs were less likely to receive approval in the first review cycle, such as eye drops or other drugs administered through the eye.

FDA has taken steps to increase the rate of generic drug approvals in the first review cycle. For example, FDA has increased communication with applicants and introduced templates for reviewers to improve the consistency and clarity of their comments. However, GAO's review of a judgmental selection of 35 applications found examples of variation in the clarity and content of FDA's comments to applicants. Such variation may have contributed to whether applicants could adequately address deficiencies within the first cycle, and therefore whether the applications were approved. In addition, stakeholders GAO interviewed expressed concern that changes to the brand-name drug's labeling mid-cycle could delay or prevent generic drugs' approval in the first review cycle, and some stakeholders said they believe that the labeling changes may be strategically timed to delay approvals. Although FDA officials noted that it would be difficult for brand-name companies to time labeling changes in this way, they said that the agency has not conducted analysis that would enable it to assess the validity of these concerns. Therefore, FDA lacks the information needed to respond to these concerns or address problems should they exist.

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Abbreviations

FDA	Food and Drug Administration
GDUFA	Generic Drug User Fee Amendments of 2012
GDUFA II	Generic Drug User Fee Amendments of 2017

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August 7, 2019

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

The Honorable Frank Pallone, Jr.
Chairman
The Honorable Greg Walden
Republican Leader
Committee on Energy and Commerce
House of Representatives

Generic drugs, which are essentially copies of approved brand-name drugs, can provide substantial cost savings for patients and third-party payers, including government health programs. According to industry estimates, in 2018 generic drugs accounted for nearly 90 percent of prescriptions filled in the United States.¹ In 2016 we reported that, on average, generic drugs have retail prices that are 75 to 90 percent lower than the retail prices of their brand-name counterparts, and new research indicates that the gap between brand-name and generic drugs may be widening.² While estimates vary, studies have found that generic drugs have collectively saved patients and third-party payers billions of dollars.³ Such cost savings have resulted in widespread national interest in facilitating the quick approval of generic drugs; however, the interest in quick approvals must be balanced by the need for safety and efficacy.

¹Association for Accessible Medicines, *2019 Generic Drug and Biosimilars Access & Savings in the U.S.*, (Washington, D.C., 2019).

²GAO, *Generic Drugs Under Medicare: Part D Generic Drug Prices Declined Overall, but Some Had Extraordinary Price Increases*, [GAO-16-706](#) (Washington, D.C.: Aug. 12, 2016).

³See GAO, *Drug Pricing: Research on Savings from Generic Drug Use*, [GAO-12-371R](#) (Washington, D.C.: Jan. 31, 2012) and Stephen W. Schondelmeyer and Leigh Purvis, *Rx Price Watch Report: Trends in Retail Prices of Generic Prescription Drugs Widely Used by Older Americans: 2017 Year-End Update*, AARP Public Policy Institute (Washington, D.C.: April 2019).

Typically, when seeking to market a generic drug in the United States, a drug sponsor who develops the drug, such as a drug company, submits a generic drug application to the Department of Health and Human Services' Food and Drug Administration (FDA) for review.⁴ Through its review, FDA seeks to determine whether the product is therapeutically equivalent to the brand-name drug. For example, a generic drug application includes data that are intended to demonstrate that the generic drug has the same active ingredient and other key characteristics and delivers the same amount of active ingredient in the same amount of time as the brand-name drug.

Questions have been raised by generic drug applicants and trade associations about the low percentage of applications approved within FDA's first review cycle—the time from when FDA accepts an application for review to when FDA makes its first decision about whether it is approved—and FDA has a stated goal to minimize the number of review cycles for applications to attain approval. If FDA finds deficiencies in the application that are not resolved during the first review cycle, then it returns the application to the applicant and informs the applicant of the deficiencies. Once those deficiencies are addressed, the applicant can amend the application and seek another full review—the second review cycle. According to FDA, in recent years (fiscal years 2013–2017) it took an average of three review cycles for a generic drug application to reach approval, which can take years, including the time it takes for the applicant to make changes to the application in response to FDA's comments and the time it takes for FDA to review the changes. While the first review cycle is typically 10 months for a standard generic drug application, each subsequent cycle can be anywhere from 3 to 10 months, according to FDA.

In response to the Generic Drug User Fee Amendments of 2012 (GDUFA), FDA committed to take steps to increase its capacity for generic drug application reviews, and in response to the Generic Drug User Fee Amendments of 2017 (GDUFA II), FDA committed to make

⁴Generic drug applications are also known as abbreviated new drug applications because they require applicants to submit less information than the corresponding brand-name drug application.

changes to its review process.⁵ These changes included commitments related to FDA's communication with generic drug applicants. FDA stated that one goal of these changes was to minimize the number of review cycles. In addition, the FDA Reauthorization Act of 2017 included a provision for us to study various issues regarding the approval of generic drug applications in the first review cycle.⁶ In this report, we examine

1. the first review cycle approval rate of generic drug applications in recent years and factors that may have contributed to whether applications were approved in the first review cycle, and
2. changes FDA has made to increase the first review cycle approval rate.

To examine the rate of generic drug applications approved during the first review cycle and factors that may have contributed to whether applications were approved in the first review cycle, we analyzed FDA data on generic drug applications that were first submitted to and reviewed by FDA in fiscal years 2015 through 2017—the most recent available data at the time of our analysis.⁷ For the purpose of our report, approvals during the first review cycle include both final and tentative approvals.⁸ The data we examined included, among other information, application characteristics such as the route of administration of the drug, the dosage form of the drug, the priority review status of the application, the number of applications submitted by the applicant in fiscal years 2015 through 2017, and the outcome of the first review cycle. Using these data, we identified the number of applications that were approved in the first review cycle and determined the rate of approval in that cycle for

⁵See Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, tit. III, 126 Stat. 993, 1008 (2012); FDA Reauthorization Act of 2017, Pub. L. No. 115-52, tit. III, 131 Stat. 1005 (2017). See also FDA, *Generic Drug User Fee Act Program Performance Goals and Procedures Fiscal Years 2013-2017*, accessed May 16, 2019, <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>. See also FDA, *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022*, accessed May 16, 2019, <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>.

⁶FDA Reauthorization Act of 2017, Pub. L. No. 115-52, § 809, 131 Stat. 1005 (2017).

⁷FDA changed how it defined the first cycle of review starting in fiscal year 2015, so the rates of approvals for prior fiscal years are not comparable.

⁸FDA grants tentative approval in situations where the generic drug application is otherwise sufficient, but patents or other exclusivities prevent final approval.

applications with certain characteristics. 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. On the basis of these steps, we determined that the data were sufficiently reliable for the purposes of our reporting objectives.

To supplement this analysis and to identify characteristics of applications that may have contributed to whether they were approved in the first review cycle, we also reviewed documentation from the first review cycle for a judgmental selection of 35 generic drug applications that were submitted to FDA in fiscal years 2017 and 2018. Specifically, we selected 30 of these applications for variation in (1) applicant size, determined by either the number of applications submitted in fiscal years 2015 through 2018 or whether the applicant had any approved applications as of fiscal year 2018, (2) application priority review status, (3) first review cycle outcome, and (4) application complexity status.⁹ We selected five additional applications that had similar characteristics to applications within our initial selection in order to review and compare comments from FDA reviewers for similar applications.

To examine changes FDA has made to increase the first review cycle approval rate, we reviewed relevant FDA guidance, regulations, and other documents related to the review and approval of generic drug applications, such as FDA's Center for Drug Evaluation and Research's *Manual of Policies and Procedures*.¹⁰ In addition, we interviewed FDA officials, including generic drug application reviewers and officials responsible for overseeing the review and approval process to learn about any changes made since the enactment of GDUFA in 2012. We

⁹Our criteria for determining applicant size differs from criteria used by FDA to determine size because the data we obtained from FDA included blinded applicant identifiers, but did not include applicant names. FDA may grant priority review status to generic drug applications under several circumstances, including for (1) first generic drugs; (2) drugs that experienced a shortage; and (3) other designations, such as for drugs that could help address public health emergencies. In accordance with its GDUFA II commitments, FDA began identifying applications as complex in fiscal year 2018, including those submitted for drugs with a complex active ingredient, formulation, or route of administration.

¹⁰FDA Center for Drug Evaluation and Research, *Manual of Policies and Procedures* (Silver Spring, Md.: 2018). Different sections of the *Manual of Policies and Procedures* are updated in different years; we reviewed the versions that were available as of the time of our work.

compared FDA's efforts to relevant standards for internal control in the federal government.¹¹

We also interviewed a non-generalizable selection of 10 stakeholders that we selected based on various criteria to obtain their views on FDA's actions to increase the first review cycle approval rate. Specifically, we interviewed officials representing five generic drug applicants selected for variation in (1) size, determined based on FDA's definition of applicant sizes for its fee structure for GDUFA II in fiscal year 2018, and (2) the types of generic drugs submitted by the applicant that had been approved in calendar years 2016-2018.¹² Some of these applicants also submitted applications for brand-name drugs. We also interviewed officials from five trade associations that represented groups involved in the generic drug application review and approval process, which we selected based on their engagement with FDA during GDUFA (in effect from October 2012 through September 2017) and the beginning of GDUFA II (in effect from October 2017 through September 2022).

We also reviewed publicly available documents related to the implementation of GDUFA and GDUFA II, such as comments submitted to www.regulations.gov, to identify perspectives of stakeholders—applicants and trade associations—related to our objectives. We supplemented the information obtained from these documents and interviews with information observed in our review of documentation from the first review cycle for 35 generic drug applications mentioned above. For four of the 35 applications, we conducted a detailed review of FDA's comments to assess the clarity of reviewers' comments to applicants and to determine how, if at all, these comments may have affected whether the applications received approval in the first review cycle. To assess the clarity of comments, we compared reviewers' comments to FDA's *Manual*

¹¹GAO, *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.

¹²FDA determined the size of the applicant for its GDUFA II fee structure based on the number of approved generic drug applications held by the applicant, including any approved applications held by the applicant's parent company, if relevant. FDA designated applicants with 5 or fewer approved applications as small, applicants with 6 to 19 approved applications as medium, and applicants with 20 or more approved applications as large.

of *Policies and Procedures*, which specifies how reviewers should communicate with applicants.¹³

We conducted this performance audit from July 2018 to August 2019 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

GDUFA

GDUFA and GDUFA II both provided supplemental resources to FDA by giving it the authority to collect user fees from the generic drug industry, in addition to its regular appropriations, in order to make improvements to the generic drug application review process.¹⁴ GDUFA was enacted in July 2012, in part, to provide funding for more generic drug application reviewers at FDA in order to handle an increase in the volume of application submissions and speed up reviews. GDUFA II was enacted in August 2017 to reauthorize the generic drug user fee program from fiscal year 2018 through fiscal year 2022. In return, FDA provided Commitment Letters to Congress that detailed its plans to implement program enhancements and meet certain performance measures related to the review of generic drug applications. For example, in its Commitment Letter for GDUFA II, FDA stated that, for applications in the first review cycle, it would review and act on at least 90 percent of them within specified timeframes—8 months for certain priority applications and 10

¹³FDA Center for Drug Evaluation and Research, *Manual of Policies and Procedures*.

¹⁴User fees are fees assessed to users for goods and services provided by the federal government. Generic drug user fees are collected and available for obligation only to the extent and in the amount provided in advance in appropriations acts.

months for all other applications.¹⁵ FDA stated that it met this performance measure for fiscal year 2018. The Commitment Letter also indicated that one of the goals of GDUFA II is to minimize the number of review cycles for applications to attain approval.

Generic Drug Application Review Process

FDA's generic drug application review process includes a number of steps. The process begins when a generic drug application is submitted to FDA for review by the Office of Generic Drugs and the Office of Pharmaceutical Quality within FDA's Center for Drug Evaluation and Research. The Office of Generic Drugs is responsible for providing regulatory oversight and strategic direction for FDA's generic drug program to make safe, effective, and high-quality generic drugs available to the public. The Office of Generic Drugs' Division of Filing Review determines whether the generic drug application is acceptable for review, meaning that the application is sufficiently complete for FDA to review the application, such as information about the amount of active ingredients present in the drug. If the generic drug application is not acceptable for review, FDA issues a Refuse to Receive letter to the applicant explaining what additional information is required before the application can be accepted for review. In response, the applicant can resubmit the generic drug application with additional information and officials within the Division of Filing Review will assess the information and determine if the resubmitted application is acceptable for review.

Once the Division of Filing Review determines that a generic drug application is acceptable for review, the first review cycle begins, and FDA officials review the application across the following three review disciplines:

¹⁵FDA may grant priority review status to generic drug applications under several circumstances, such as for drugs that experienced a shortage. A priority generic drug application may receive a review approval timeline of 8 months, rather than 10, if the applicant communicates certain information to FDA. See 21 U.S.C. § 355(j)(11). See also FDA, *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022*, accessed May 16, 2019, <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>.

FDA will refuse to receive a generic drug application if it determines that the application is not acceptable because it is not sufficiently complete for a substantive review.

- **Bioequivalence.** Officials within the Office of Bioequivalence are responsible for examining whether the generic drug application is bioequivalent to the brand-name drug, meaning that the drug delivers the same amount of active ingredient in the same amount of time as the brand-name drug.
- **Labeling.** Officials within the Division of Labeling Review are responsible for ensuring that the proposed labeling language in the generic drug application, including the drug's prescribing information, matches the language found in the labeling of the corresponding brand-name drug.¹⁶
- **Pharmaceutical quality.** Officials within the Office of Pharmaceutical Quality have responsibility for ensuring the quality of drug products and assessing all drug manufacturing facilities, including both domestic and foreign. Officials within this office assess the risk of toxic substances or bacterial content in the drug, among other things.

All generic drug applications are reviewed by primary reviewers and secondary reviewers. Primary reviewers assess the application to ensure that the documentation meets regulatory requirements in their specific disciplines. For example, primary reviewers within the Office of Pharmaceutical Quality evaluate documentation related to the proposed drug manufacturing process to ensure that the process produces quality drugs consistently. Secondary reviewers ensure the quality and consistency of primary reviewers' assessments and the clarity of communication to applicants.

During the first review cycle, FDA communicates with applicants when issues arise during its review that may prevent the agency from approving the generic drug application. This communication is typically made through the issuance of information requests or discipline review letters:

- **Information requests.** Information requests are letters sent to applicants to request clarification or additional information that is needed or would be helpful for FDA to complete its review. These letters may be sent by any review discipline and can be sent at any point after the Office of Generic Drugs accepts the generic drug application for review.

¹⁶Generic drug applications must include copies of their proposed labeling, which generally must match the corresponding brand-name drug labeling, with some exceptions. 21 C.F.R. § 314.94(a)(8) (2018).

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- **Discipline review letters.** Discipline review letters are letters issued by each review discipline at about the mid-point of the review cycle to identify possible deficiencies. FDA officials said they aim to issue these letters no later than 6 months into the first review cycle.¹⁷

In response to these letters, applicants can submit additional information for FDA to consider before the end of the review cycle.

After FDA's three review disciplines complete their review of an application and any additional information the applicant has submitted in response to information requests and discipline review letters, the agency issues an action letter that informs the applicant of whether the application is approved, marking the end of the first review cycle and the end of FDA's review if the application is approved. There are three types of action letters:

- **Approval letter.** Issued 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.** Issued when the agency has completed its review of an application and has concluded that the generic drug application is sufficient, but patents or other exclusivities prevent approval. A tentative approval letter does not allow the applicant to market the generic drug.
- **Complete response letter.** Issued at the completion of the review of an application where deficiencies remain at the end of the review cycle. The complete response letter describes any deficiencies that must be corrected in order for the application to be approved.

For a generic drug application that receives a complete response letter, the applicant can amend the application and seek another full review, which begins the second or subsequent review cycles. During these cycles, FDA officials review changes made to generic drug applications in response to deficiencies that FDA identified.

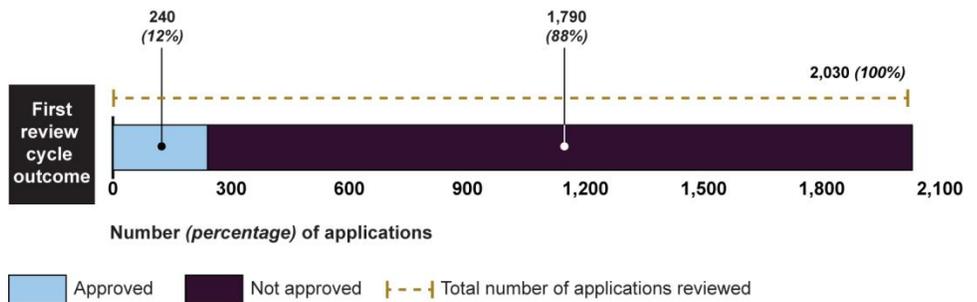
FDA Approved 12 Percent of Generic Drug Applications in the First Review Cycle and

¹⁷FDA officials noted that if an information request was issued very close to the time that the discipline review letter would have otherwise been sent, a discipline review letter may not be issued.

Several Factors May Have Contributed to Whether Applications Were Approved

Our analysis of FDA data shows that 12 percent of the 2,030 generic drug applications that FDA reviewed in fiscal years 2015 through 2017 received approval in the first review cycle.¹⁸ See figure 1.

Figure 1: Number and Percentage of Generic Drug Applications Approved in the First Review Cycle, Fiscal Years 2015–2017



Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-19-565

Note: For purposes of this report, approvals in the first review cycle include both final and tentative approvals. Tentative approval is given in situations where the generic drug application is otherwise sufficient, but patents or other exclusivities prevent final approval. Of the 240 approvals, 187 were final and 53 were tentative. Our calculation of the rate of approvals excludes applications for which FDA did not complete the first review cycle, including pending, withdrawn, and canceled applications.

We identified several factors, including certain characteristics of generic drug applications, that may have contributed to whether an application received approval in the first review cycle, including the sufficiency of the application, deficiencies in drug quality, the type of drug reviewed, and the application’s priority status.

Sufficiency of the application. We found that the sufficiency of the generic drug application, including the completeness of the application and the degree to which the applicants understood and fulfilled

¹⁸For the purpose of our report, approvals in the first review cycle include both final and tentative approvals. Tentative approval is given in situations where the generic drug application is otherwise sufficient, but patents or other exclusivities prevent final approval. FDA clarified its definition of the first review cycle starting in fiscal year 2015, so the rates of approvals for prior fiscal years—including in the first 2 years of GDUFA (fiscal years 2013 and 2014)—are not comparable to the rates in fiscal year 2015 through 2017. Our calculation of the rate of approvals excludes generic drug applications for which FDA did not complete the first cycle of review, including pending, withdrawn, and canceled applications.

application requirements, affected its likelihood of receiving an approval in the first review cycle. According to FDA, one indication of the sufficiency of the generic drug application is whether FDA had previously refused to receive the application for review because it was not substantially complete upon its first submission. Our analysis of FDA data found that applications that had previously been refused were slightly less likely to be approved in the first review cycle compared with applications that had not previously been refused, and rates of approvals decreased for applications with two previously refused attempts. See table 1.

Table 1: Approval in the First Review Cycle for Generic Drug Applications by Number of Times the Food and Drug Administration (FDA) Previously Refused to Receive the Application, Fiscal Years 2015–2017

n/a	n/a	Applications that received approval in the first review cycle ^b	
		Number	Percentage
Number of previous refuse to receive responses ^a	Total applications reviewed		
0	1,753	213	12
1	251	25	10
2 ^c	26	2	8
All applications	2,030	240	12

Source: GAO analysis of FDA data. | GAO-19-565

^aFDA will refuse to receive a generic drug application if it determines that the application is not acceptable because it is not substantially complete to permit a substantive review.

^bFor purposes of this report, approvals in the first review cycle include both final and tentative approvals. Tentative approval is given in situations where the generic drug application is otherwise sufficient, but patents or other exclusivities prevent final approval.

^cNo applications in our dataset had more than two refuse to receive responses.

According to stakeholders we interviewed, the sufficiency of a generic drug application may partially reflect the level of experience the applicant has in submitting applications, and we found some evidence to support this explanation. FDA managers and reviewers said that, in general, less experienced applicants are more likely to produce lower-quality generic drug applications compared to applicants with relatively more experience. Our analysis of FDA data found that applicants that submitted just one application during fiscal years 2015 through 2017 had a slightly lower rate of approval in the first review cycle (10 percent) compared to the rate across all applicants (12 percent).¹⁹ Additionally, in our review of 35

¹⁹Out of the 2,030 generic drug applications submitted during fiscal years 2015 through 2017, there were 277 unique applicants; 114 of these applicants submitted just one application during these years.

selected generic drug applications, we identified three applications that were from applicants that had no previously approved generic drug application submissions, an indication that they may have little or no experience with these applications. None of the three applications were approved in the first review cycle. One of these applications elicited reviewer comments that outlined basic application requirements, potentially reflecting the lack of experience of the applicant.

Drug quality deficiencies. Our review of documentation from the first review cycle for 35 generic drug applications included 26 that were not approved in that cycle. Among those 26 applications, the most common deficiencies that remained at the end of the first cycle were related to the quality of the drug—356 out of 435 deficiencies. These deficiencies included issues related to the drug manufacturing facilities, which can affect the quality of the drug produced and the stability of the drug over time, among others. Officials from one large applicant told us that most of the comments they received from FDA reviewers are related to the quality of the drug. Three out of five applicants we interviewed also noted that the results from inspections of drug manufacturing facilities—which FDA includes as a component of its review of the quality of the drug—are a factor that may cause an application not to be approved in the first review cycle. Among the 26 applications we reviewed that were not approved, eight had an outstanding deficiency related to the manufacturing facility.²⁰

Type of drug. We also found that the rate of approval in the first review cycle differed based on certain characteristics of the type of drug reviewed, including the route of administration, which may indicate the complexity of the drug. Complexity can also be influenced by other factors including, for example, the drug’s active ingredient or formulation.²¹ FDA officials noted that some complex drugs—including those that combine drug products with drug delivery devices, such as asthma inhalers—are less likely to be approved in the first review cycle. Officials we interviewed from one large applicant—which we identified based on the number of approved generic drug applications it had in fiscal year 2018—reported

²⁰Facility deficiencies automatically result in a “major” deficiency—meaning that the next review cycle is an additional 6 to 10 months, as compared to an additional 3 months for a “minor” deficiency.

²¹According to FDA’s GDUFA II commitments, drugs may be considered complex for a variety of reasons, including due to the drug’s active ingredients, routes of administration, dosage forms, drug-device combinations, and uncertainty concerning how the generic drug application will be approved.

that their company had never submitted a generic drug application for a complex drug product that received approval in the first review cycle despite having significant experience with producing complex drugs. Officials we interviewed from another applicant said that very few of its dermatological products, which are considered complex, had received approval in the first review cycle.

In our review of FDA data, we also found that applications for drugs with certain routes of administration—the method by which the drug is taken, such as oral, topical, or intravenous—had different rates of approval in the first review cycle. In particular, from fiscal years 2015 through 2017, FDA reviewed generic drug applications for 41 ophthalmic and 20 transdermal drugs—types of drugs that FDA considers complex—and none of these applications received approval in the first review cycle.²² In contrast, generic drug applications for topical drugs, which FDA also identifies as complex, had higher approval rates. Specifically, our analysis found that the rate of approvals in the first review cycle for generic drug applications for topical drugs was 25 percent—more than double the rate for all applications included in our analysis. FDA officials stated that in recent years FDA released several product-specific guidances for topical drugs—technical guidance intended to help applicants identify the most appropriate methodology for developing certain drugs and generating the evidence needed to gain approval. FDA officials told us these guidances may have contributed to the higher rates of approval in the first review cycle for topical drugs. See table 2.

Table 2: Approval in the First Review Cycle for Generic Drug Applications by Route of Administration, Fiscal Years 2015–2017

n/a Drug routes of administration	n/a Total applications reviewed	Applications that received approval in the first review cycle ^a	
		Number	Percentage
Topical	205	52	25
Ophthalmic ^b	41	0	0
Transdermal ^c	20	0	0

²²Ophthalmic drugs are administered through the eye, such as eye drops, and transdermal drugs are administered through the skin, such as skin patches. FDA noted that a drug with a certain route of administration may be considered complex for other reasons, such as its dosage form.

n/a	n/a	Applications that received approval in the first review cycle ^a	
		Number	Percentage
Drug routes of administration	Total applications reviewed		
All other routes of administration	1,764	188	11
All applications	2,030	240	12

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-19-565

^aFor purposes of this report, approvals in the first review cycle include both final and tentative approvals. Tentative approval is given in situations where the generic drug application is otherwise sufficient, but patents or other exclusivities prevent final approval.

^bOphthalmic drugs are administered through the eye, such as eye drops.

^cTransdermal drugs are administered through the skin, such as skin patches.

Generic drug application priority review designation. In addition, we found that a generic drug application’s priority review status may affect the rate of approval in the first review cycle. FDA may grant priority review status to applications under several circumstances, including for the first generics of brand-name drugs and other designations, such as for drugs that could help address public health emergencies. Our analysis of FDA data found that the rates of approval in the first cycle were lower for applications for first generics than for applications with no priority designation—6 percent and 14 percent, respectively. One potential explanation for the relatively low rate of approval is that for a first generic, applicants have a financial incentive to be the first to submit an application to FDA. Officials from one trade association stated that applications for first generics may be of lower quality because the applicants are rushing to submit their applications.²³ In other cases, priority designations were associated with higher first-cycle approval rates. First-cycle approval rates for applications with other types of priority designations were higher than for applications with no priority designation—18 percent for applications that were marked as priority for other reasons, such as drug shortages or public health emergencies. See table 3.

²³Under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Amendments, the first applicant to submit a substantially complete generic drug application that makes certain certifications relating to the status of the brand-name drug’s patents may obtain the exclusive right to market the generic drug for a period of 180 days. See Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355(j)(5)(B)(iv)).

Table 3: Approval in the First Review Cycle for Generic Drug Applications by Priority Review Status, Fiscal Years 2015–2017

Priority review status	Total applications reviewed	Applications that received approval in the first review cycle ^a	
		Number	Percentage
Applications with a first generic priority designation ^b	516	32	6
All other applications with priority designations	66	12	18
Applications with no priority designation	1,448	196	14
All applications	2,030	240	12

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-19-565

^aFor purposes of this report, approvals in the first review cycle include both final and tentative approvals. Tentative approval is given in situations where the generic drug application is otherwise sufficient, but patents or other exclusivities prevent final approval.

^bThis category includes all applications that have been granted a first generic priority designation. Some of these applications may have other designations as well, such as drug shortage designations.

FDA Made Changes That Could Increase the Rates of Approval for Generic Drugs in the First Review Cycle, but Opportunities Exist to Enhance Its Efforts

FDA Has Taken Steps to Enhance Communication with Applicants and Improve Reviewer Consistency to Increase the Rate of Generic Drug Approvals in the First Review Cycle

Our review of FDA guidance and regulations found that FDA has taken steps to enhance communication with applicants to increase the rate of generic drug application approvals in the first review cycle. Specifically, since the beginning of fiscal year 2013 in response to GDUFA, FDA increased communication with applicants prior to and during a generic drug application's first review cycle consistent with its goal of helping applicants prepare approvable applications. These changes have included the following:

- **Additional product-specific guidance.** FDA has continued to release new and revised product-specific guidance to support a generic drug application's approval within the first review cycle. Since GDUFA's implementation and at the time of our review, FDA told us that it issued 993 new and revised product-specific guidance documents that describe acceptable methodologies for developing generic drugs and generating evidence needed to support a generic drug application's approval.²⁴ FDA officials indicated that product-specific guidance helps streamline both application development and review.
- **Additional regulatory guidance.** FDA has also issued regulatory guidance to communicate the agency's expectations for the content and format of generic drug applications, which can facilitate approval in the first review cycle. In addition, in 2018, FDA issued draft

²⁴FDA maintains a public website that allows users to search for product-specific guidance documents. For more information, see FDA, *Product-Specific Guidances for Generic Drug Development*, accessed May 6, 2019, <https://www.fda.gov/drugs/guidances-drugs/product-specific-guidances-generic-drug-development>.

guidance that described common application deficiencies and sought to promote approval during the first review cycle by providing recommendations on avoiding these recurring deficiencies.²⁵

- **Presentations to industry.** In presentations to applicants and others, FDA officials have presented information about generic drug application reviews and deficiencies frequently identified in generic drug applications. FDA has posted some of these presentation materials, including several video recordings, publicly on its website to share the information with industry.²⁶
- **Communication during the review cycle.** FDA has changed its review process to encourage reviewers to communicate with applicants at about the mid-point of the review cycle. FDA reviewers now aim to issue discipline review letters at about the mid-point of the first review cycle, rather than waiting until the end of the review cycle to communicate deficiencies. According to FDA, these earlier communications are intended to provide applicants with an opportunity to address issues before the end of the first review cycle and facilitate more approvals during that cycle.
- **Assistance with applications for complex drugs.** FDA has taken steps to assist applicants developing generics of complex drugs, such as drugs with complex active ingredients, formulations, or routes of administration. Beginning in fiscal year 2018 when GDUFA II was implemented, applicants developing complex drugs may request meetings with FDA prior to submitting a generic drug application and at the mid-point of the review cycle.²⁷ In addition, FDA officials told us that since fiscal year 2013 when GDUFA was implemented, the agency has released 378 product-specific guidance documents focused on complex drugs.

While all five applicants we interviewed generally described FDA's efforts to increase communication as helpful, they offered opportunities for improvement. For example, four out of the five applicants said that

²⁵FDA Center for Drug Evaluation and Research, *Good ANDA Submission Practices: Guidance for Industry* (Silver Spring, Md.: 2018).

²⁶See FDA, *Meeting Presentations (Drugs)*, accessed May 17, 2019, <https://www.fda.gov/about-fda/center-drug-evaluation-and-research/meeting-presentations-drugs>.

²⁷For more information, see FDA Center for Drug Evaluation and Research, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA Guidance for Industry* (Silver Spring, Md.: 2017).

product-specific guidance helps them understand exactly what the requirements are for product development, which can facilitate approval in the first review cycle. However, two of these applicants also said that FDA does not obtain sufficient input from the generic drug industry when developing product-specific guidance documents. To increase transparency, stakeholders said that FDA could solicit industry input to avoid proposing unrealistic guidance and one stakeholder suggested that FDA could create a workgroup to prevent unintended consequences following the implementation of new and revised guidance. However, FDA officials told us that draft guidance documents have a public comment period for stakeholders to provide comments on guidances before they are finalized.

In December 2017, we similarly found that stakeholders indicated they would benefit from greater transparency in FDA's process for developing guidance.²⁸ We recommended that FDA publicly announce the agency's plans for issuing new and revised product-specific guidance for nonbiological complex drugs within the next year. FDA agreed with this recommendation and published a website in April 2019 that provides information about upcoming product-specific guidance documents for complex generic drugs.²⁹

In addition, all five applicants we interviewed said that FDA has improved communication with them, such as by increasing the frequency and timing of communications, and two applicants indicated that discipline review letters add predictability to the review process. (See app. I for more information on FDA's changes to the generic drug application review process to improve communication with applicants.) While all five applicants we interviewed generally agreed that the increased communications would help increase rates of first-cycle approval, they also suggested that additional flexibility to communicate with FDA informally mid-cycle, such as by phone, could further facilitate the review process by helping applicants respond to questions or get clarity on questions included in the information requests or discipline review letters.

²⁸See GAO, *Generic Drugs: FDA Should Make Public Its Plans to Issue and Revise Guidance on Nonbiological Complex Drugs*, GAO-18-80 (Washington, D.C.: Dec. 14, 2017).

²⁹For more information, see FDA, "Upcoming Product-Specific Guidances for Complex Generic Drug Product Development," accessed May 14, 2019, <https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-complex-generic-drug-product-development>.

FDA officials told us that applicants currently can request teleconferences with FDA, such as after receiving a complete response letter; however, they also noted that applicants generally prefer email communications and such teleconferences are not frequently utilized.

FDA has also taken steps to improve consistency among reviewers. These steps could facilitate more approvals in the first review cycle because receiving consistent comments from FDA reviewers typically makes it easier for applicants to respond more quickly, which—according to some stakeholders—can result in approval in the first review cycle. These changes include the following:

- **Creating review templates.** Officials from FDA’s review disciplines have developed templates to guide reviewers through the generic drug application review process. According to FDA’s *Manual of Policies and Procedures*, these templates are intended to increase reviewers’ efficiency and improve assessment consistency.³⁰
- **Developing common phrases.** FDA also issued internal guidance on common phrases that reviewers may use to communicate generic drug application deficiencies in their comments to applicants during the first review cycle. For example, officials from the Division of Labeling Review said they maintain a database of common phrases and train reviewers on how to explain deficiencies to applicants. Officials explained that the Division of Labeling Review is also working toward pre-populating some parts of the review template to increase efficiency and consistency in the review process.
- **Understanding the generic drug industry.** FDA has taken steps to increase reviewers’ and applicants’ common understanding of industry practices and FDA review standards, such as through visits to manufacturing facilities, to improve the quality and consistency of reviewers’ comments in the first review cycle. However, all five applicants we interviewed noticed inconsistency among reviewers. FDA officials and two applicants suggested that this may be because FDA reviewers have different professional backgrounds. One applicant noted that some reviewers benefit from visiting manufacturing facilities if they do not have prior experience in the generic drug industry. Officials from a trade association said that such steps improve applicants’ understanding of what FDA reviewers are

³⁰FDA Center for Drug Evaluation and Research, *Manual of Policies and Procedures*.

looking for in generic drug applications and may enhance their ability to submit applications that are approvable in the first review cycle.

Opportunities Exist to Enhance FDA's Efforts to Increase the Rates of Approval for Generic Drugs in the First Review Cycle

While stakeholders stated that the changes FDA made to improve reviewer consistency were positive, they noted that inconsistency among reviewers still remained, and we also found inconsistencies among reviewers. In addition, while stakeholders we interviewed raised concerns that the timing of brand-name labeling changes could affect whether applications were approved in the first review cycle, FDA has not taken steps to assess the validity of these concerns.

Inconsistency among FDA reviewers. While FDA has taken steps to improve consistency among generic drug application reviewers, stakeholders noted that inconsistencies persist, and these inconsistencies may influence whether an application is approved during the first review cycle. For example, most stakeholders we interviewed (three out of five trade associations and four out of five applicants) indicated that they were aware of examples when different FDA reviewers within the same review discipline provided substantively different assessments of similar generic drug applications, specifically by requesting additional information from applicants for some applications and not others. For example, one applicant cited an example of two similar topical drugs whose applications relied on the same data set. The reviewer for one application required additional data, while the reviewer for the other application did not. To improve consistency, four applicants we interviewed suggested that FDA improve its reviewer training and one suggested that FDA create a workgroup to examine and address inconsistencies among reviewers.

Four of the five applicants we interviewed also reported variation in the consistency of reviewers' comments, including a lack of clarity in the information required for the applicant to address the comments. For example, one applicant said that they have received comments where reviewers did not specify what further information was required, and added that comments that suggest specific resolutions are extremely helpful, which would be consistent with FDA's *Manual of Policies and Procedures*. This manual describes a standard process for FDA reviewers to use when assessing the completeness of generic drug applications, including clearly communicating with applicants about

deficiencies that must be corrected for their applications to be approved in order to reduce the number of review cycles.³¹ According to the manual, primary reviewers are responsible for assessing whether applications meet the regulatory requirements for approval, while secondary reviewers are responsible for ensuring consistency among assessments and quality of communications to the applicant. Further, the manual advises primary and secondary reviewers to ensure that comments to applicants about deficiencies include similar content. The manual also indicates that comments should include the following four elements: (1) refer to a specific location within the generic drug application; (2) identify the omitted information or explain the problem with the information submitted; (3) explain the actions necessary to resolve the deficiency; and (4) explain why the information or revision is needed. Finally, FDA provides reviewers with plain language writing guidelines and other writing resources to support the development of clear messages for external communications.³²

In our review of documentation from the first review cycle for 35 generic drug applications, we found variation in the clarity and specificity of some reviewer comments that may have influenced the outcome of the first review cycle. For example, some discipline review letters included clear descriptions of potential remedies for some deficiencies, while others did not clearly describe the deficiency or FDA's expectations for an approvable generic drug application. Of the 35 generic drug applications, we conducted a more detailed review of four applications from fiscal year 2018—two that received approval in the first review cycle and two that did not. In the two applications that were not approved in the first review cycle, we identified 32 instances in which the comments did not fully meet FDA's criteria.

Two of the four applications we reviewed in more detail had similar numbers and types of deficiencies identified in the discipline review letters sent to the applicants mid-way through the first review cycle, such as quality deficiencies related to the drug substance and drug product, but the clarity and content of the comments included in the discipline review

³¹FDA Center for Drug Evaluation and Research, *Manual of Policies and Procedures*.

³²The Plain Writing Act of 2010 was signed into law on October 13, 2010, and requires federal agencies to use plain language whenever they communicate with the public. Pub. L. No. 111-274, 124 Stat. 2861 (2010). In response, FDA created plain language guidance for employees, *Putting It Plainly: Getting Started with Plain Language at FDA* (Silver Spring, Md.: 2018).

letters varied considerably. For one of the applications, the comments were written clearly and, consistent with FDA’s *Manual of Policies and Procedures*, identified options for addressing the deficiencies. For the other application, the comments were less clear and did not clearly identify ways to address the deficiencies. The applicant of the generic drug application with clearly written comments resolved all of the deficiencies raised in their discipline review letter and the generic drug application was approved in the first review cycle. In contrast, the applicant of the other application did not resolve all deficiencies raised in their discipline review letter and was not approved in the first cycle. See Table 4 for more detail on these two examples.

Table 4: Examples of Food and Drug Administration (FDA) Reviewer Comments to Applicants for Two Generic Drug Applications That FDA Reviewed in Fiscal Year 2018

n/a	Example 1	Example 2
First review cycle outcome	Approved	Not approved
Number of deficiencies identified in the middle of the first review cycle	31	32
Description of reviewer’s comment	FDA clearly outlined several options for addressing a deficiency to the applicant in the middle of the first review cycle, and also proactively recommended that the applicant report additional information related to a component of the application that was still pending FDA review.	FDA’s communications to the applicant included a description of a deficiency by the reviewer, but did not clearly identify the actions the applicant must take to address the deficiency.
Applicant’s response	The applicant addressed this deficiency and all other identified deficiencies, and the application was approved at the end of the first review cycle.	The applicant responded to FDA’s comments, but did not provide adequate information to address the deficiency. The application was not approved at the end of the review cycle, and the complete response letter requested additional information about this deficiency.
Deficiencies identified in the middle of the review cycle that remained at the end of the first cycle	0	9

Source: GAO analysis of FDA documents. | GAO-19-565

Inconsistency among reviewers could affect the rate of approvals in the first review cycle if comments provided to applicants differ in content or are not clearly communicated. For example, if some reviewers provide unclear comments, it could be more difficult for the applicant to address deficiencies in a timely manner, while applicants that received clear comments could potentially address deficiencies within the first review cycle. This could delay some generic drugs from entering the market if applicants require more time, including potentially additional FDA review

cycles, to understand and respond to unclear comments. This has potential impacts on patient access to generic drugs and on applicants' abilities to effectively manage their expectations for when their generic drug applications will be approved.

FDA officials explained that although secondary reviewers are experienced, they do not consistently receive additional training to ensure clarity and consistency among primary reviewers. They noted that FDA offers training in clear writing for FDA employees but it is not required for reviewers. FDA managers noted that some inconsistency among reviewers may persist due to various factors such as tenure with the agency and different professional backgrounds or interpretations of the generic drug application information. They also said that standardizing reviewers' writing is challenging since each reviewer might have his or her own writing style and scientific expertise. Two applicants and one trade association we interviewed also said that the length of reviewers' tenure with the agency could impact the substance of their comments in information requests and discipline review letters and the likelihood of the applicant attaining approval in the first review cycle. For example, one trade association we interviewed said that inexperienced reviewers typically request information from applicants that a more experienced reviewer would already know, such as information about drug manufacturing facilities.

Unknown effects of labeling changes. Three applicants we interviewed noted that they believe FDA could improve the rate of approvals during the first review cycle if they took steps to mitigate delays that stakeholders said result from brand-name drug labeling changes that occur mid-cycle. Because generic drug labels generally must match brand-name labels, most applicants we interviewed said that changes made by brand-name drug companies to the labeling of drugs during the review process can delay or prevent approval of generic drugs in the first review cycle because the applicant of the generic drug would likely need to update the label before it is approved.³³ In addition, five of the 10 stakeholders we interviewed said they believe such labeling changes negatively impact the rate of first-cycle approvals, and three said they believe that brand-name companies may strategically time updates to a

³³Certain differences between generic drug labeling and corresponding brand-name drug labeling may be permitted. See 21 C.F.R. § 314.94(a)(8) (2018).

brand-name drug's labeling to occur right before the approval of a generic competitor in order to delay generic drug approvals.

Although our review of 35 selected applications did not identify examples where labeling changes made during the first review cycle were the only factor that prevented approval, we identified two instances where labeling changes were among multiple factors that prevented approval. Specifically, we identified two applications for which the complete response letters noted recent changes in the brand-name drug's labeling as one of multiple factors that contributed to the generic drug application's failure to receive approval in the first review cycle. One of these applications had successfully addressed several labeling deficiencies during the first review cycle, but received a complete response letter that included new labeling deficiencies because of recent changes in the brand-name drug's labeling.

Three applicants and one trade association identified labeling changes as a concern during our interviews. Two of these applicants and the trade association suspected updates are strategically timed to delay generic drug approvals. However, FDA does not know whether there is validity to these concerns because it has not conducted analysis that would enable it to assess their validity. FDA officials noted that they were aware of these types of concerns, but thought it would be difficult for brand-name drug companies to successfully time changes in their drugs' labeling to affect applications under review, and that labeling changes for brand-name drugs must be justified, for example, to note an adverse reaction identified after approval. However, FDA officials also acknowledged that there may be an incentive for brand-name drug companies to change the label on a drug frequently to make it more difficult for a generic drug application to be approved.

FDA officials stated that the Office of Generic Drugs does not assess how often brand-name companies change their labeling or track how often such labeling changes occur because such changes are reviewed by the Office of New Drugs. Further, while FDA officials noted that the two offices have coordinated on the review of some labeling changes, they stated that they do not coordinate on the timing of approval of brand-name drug label changes. This is inconsistent with federal internal control standards, which state that agencies should identify risks that affect their defined objectives and use quality information to achieve these objectives, including by identifying the information required to achieve the

objectives and address related risks.³⁴ In addition, FDA can approve a generic drug application even though changes have been made in the brand-name drug labeling that the applicant has not incorporated into its proposed labeling, provided the applicant meets certain criteria; however, FDA officials told us that applications rarely meet the required criteria.³⁵ Conducting an assessment of the extent to which the timing of such changes affect the approval of generic drugs in the first cycle of review would provide FDA with the necessary information to respond to stakeholder concerns and take action, as appropriate, such as by coordinating with the Office of New Drugs on this issue. To the extent that brand-name companies' labeling changes are creating unnecessary delays in generic drug approval, such delays may impede generic drug entry into the market, which would be inconsistent with FDA's stated goals of speeding up generic drug reviews.

Conclusions

The timely approval of safe generic drugs in FDA's first review cycle can provide substantial cost savings to patients and third-party payers. Since the enactment of GDUFA, FDA has taken steps to help applicants submit stronger generic drug applications and correct deficiencies within the first review cycle. However, according to FDA its most recent analysis found that the average generic drug application required three cycles of review before approval. Opportunities exist to enhance FDA's efforts to increase the rates of approval for generic drugs in the first review cycle, including improving the consistency and clarity of reviewer comments and assessing the effects of the timing of brand-name companies' changes to labeling.

Taking such steps could help FDA meet the agency's goals of minimizing the number of review cycles necessary for generic drug application approval and increasing the overall rate of approval, including within the

³⁴[GAO-14-704G](#).

³⁵The Federal Food, Drug, and Cosmetic Act sets forth the following criteria for approval of a generic drug application under such circumstances: (1) FDA approved a revision to the labeling of the brand-name drug within 60 days of the expiration of a patent or exclusivity, (2) the revision does not include a change to the "Warnings" section of the label, (3) the generic drug applicant agrees to submit revised labeling to match the brand-name drug's labeling within 60 days, and (4) the generic drug application otherwise meets applicable requirements for approval. 21 U.S.C. § 355(j)(10). See also FDA Center for Drug Evaluation and Research, *Manual of Policies and Procedures*.

first review cycle. Increasing the rate of approval in the first review cycle, while maintaining the efficacy and safety of generic drugs, can expand consumer access to relatively lower cost medications and has the potential to save patients and third-party payers billions of dollars.

Recommendations for Executive Action

We are making the following two recommendations to FDA.

The Commissioner of FDA should take additional steps to address inconsistency in its written comments to generic drug applicants—including the clarity of writing and the content of comments—among reviewers, such as requiring additional training for reviewers. (Recommendation 1)

The Commissioner of FDA should assess the extent to which the timing of brand-name drug companies' drug labeling changes affect the approval of generic drug applications in the first review cycle, and take steps, as appropriate, to limit the effect of brand-name drug labeling changes on pending generic drug applications. (Recommendation 2)

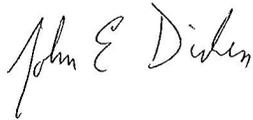
Agency Comments

We provided a draft of this report to HHS for review and comment. In its written comments, which are reproduced in appendix II, HHS concurred with our recommendations. HHS stated that it will take steps to improve the clarity and content of primary reviewers' comments by, for example, providing training on written communication. Additionally, HHS stated that it will take steps to assess examples in which a brand-name drug company labeling change impacted the timeline of a generic drug approval and assess what actions could address this issue. In addition, HHS provided technical comments, which we incorporated as appropriate.

We are sending copies of this report to the congressional addresses, the Secretary of Health and Human Services, and other interested parties. In addition, the report is available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff have any questions about this report, please contact me at 202-512-7114 or dickenj@gao.gov. Contact points for our Offices

of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix III.

A handwritten signature in black ink that reads "John E. Dicken". The signature is written in a cursive style with a large, stylized 'J' and 'D'.

John E. Dicken
Director, Health Care

Appendix I: Changes to the Generic Drug Review Process to Improve Communications with Applicants

The Food and Drug Administration (FDA) made several changes to its review process for generic drug applications in its implementation of the Generic Drug User Fee Amendments of 2017 (GDUFA II) that are intended to improve communications with applicants, such as drug companies, and included the following:

- **Additional communication with applicants.** In its GDUFA II Commitment Letter to Congress,
 1. FDA committed to notify applicants of potential deficiencies in an application that could prevent approval in the first review cycle through information requests or discipline review letters by about the mid-point of the review cycle;¹ and
 2. FDA committed to continue to issue additional information requests or discipline review letters late in the review cycle as needed, and, in certain circumstances, to work beyond the review timeframe to issue an approval.
- **Pre-submission facility correspondence.** In its GDUFA II Commitment Letter to Congress, FDA committed to communicating with applicants of priority generic drug applications before the

¹Information requests are letters sent to applicants to request clarification or additional information that is needed or would be helpful for FDA to complete its review. Discipline review letters are letters issued by each of FDA's review disciplines at about the mid-point of the review cycle to identify preliminary deficiencies for applicants to address.

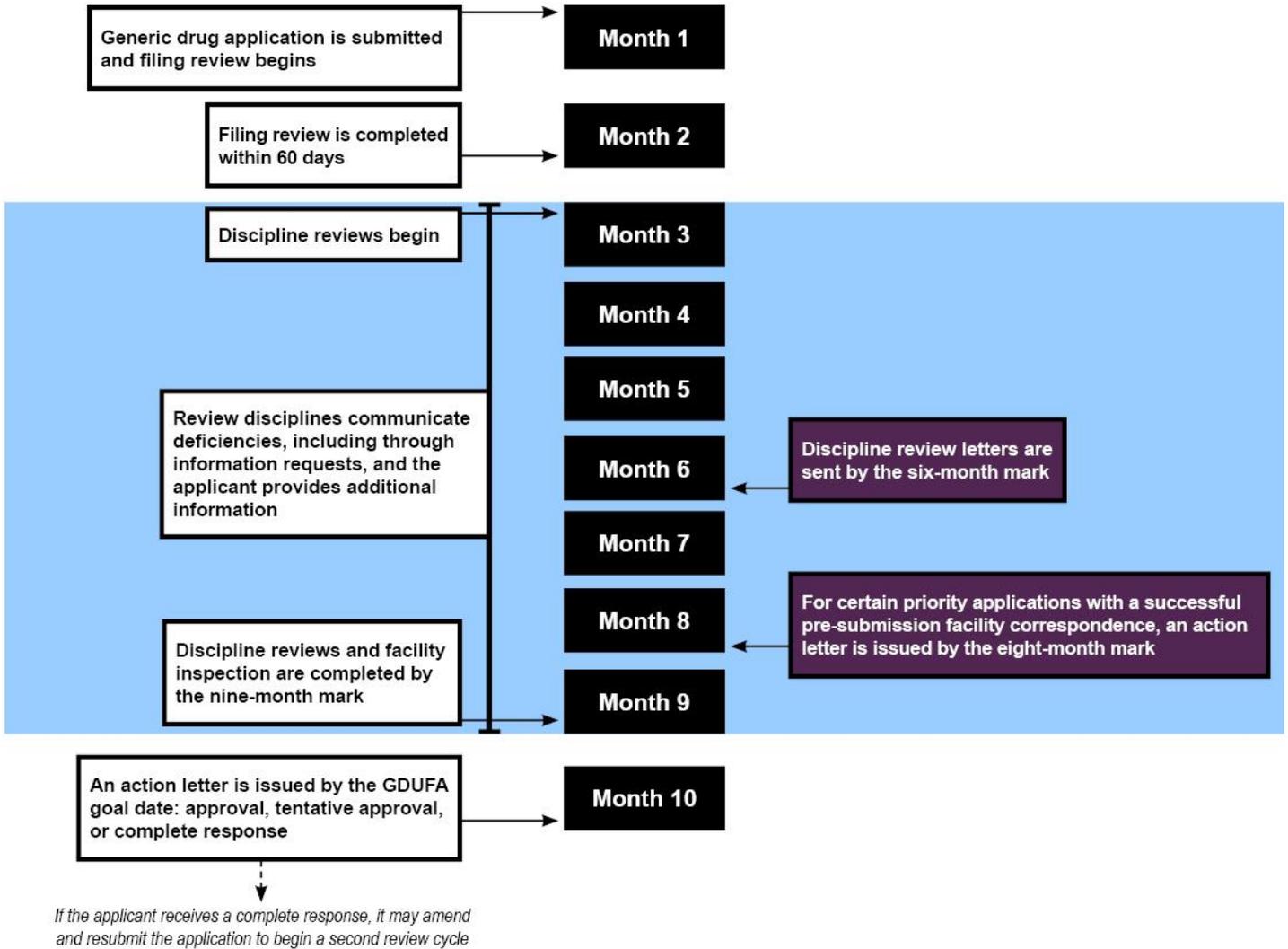
application is submitted.² For priority generic drug applications, FDA accepts information about facilities associated with an application, such as manufacturing facilities, at least 2 months before the application is submitted. If FDA finds the pre-submission facility correspondence includes complete and accurate information, the application may receive a review timeline of 8 months, rather than 10.³

Figure 2 provides an overview of the timeline for the first review cycle for generic drug applications under the Generic Drug User Fee Amendments of 2012 (GDUFA) and the revised review process under GDUFA II.

²FDA may grant priority review status to generic drug applications under several circumstances, including for (1) first generic drugs; (2) drugs that experienced a shortage; and (3) other designations, such as for drugs that could help address public health emergencies.

³21 U.S.C. § 355(j)(11). See also FDA, *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022*, accessed May 16, 2019, <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>.

Figure 2: Overview of the Food and Drug Administration’s (FDA) Timeline and Review Process for the First Review Cycle for Generic Drug Applications since the Enactment of the Generic Drug User Fee Amendments of 2012 (GDUFA) and Its Reauthorization in 2017 (GDUFA II)



Communication on a rolling basis
 GDUFA and GDUFA II milestone
 GDUFA II milestone

Source: GAO analysis of FDA documents. | GAO-19-565

Note: FDA aims to review non-priority generic drug applications within 10 months. FDA may grant priority review status to generic drug applications under several circumstances, including for (1) first generic drugs; (2) drugs that experienced a shortage; and (3) other designations, such as for drugs that could help address public health emergencies. Applicants with priority generic drug applications may communicate with FDA 2 months before the application is submitted to facilitate FDA’s review. An 8-month priority review may be granted for priority generic drug applications with pre-submission correspondence that includes complete and accurate facilities information at least 2 months before

**Appendix I: Changes to the Generic Drug
Review Process to Improve Communications
with Applicants**

submission of the application. See 21 U.S.C. § 355(j)(11). See also FDA, *GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022*, accessed May 16, 2019, <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>.

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

**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

JUL 17 2019

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 Applications: FDA Should Take Additional Steps to Address Factors that May Affect Approval Rates in the First Review Cycle*" (GAO-19-565).

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

Sincerely,

A handwritten signature in blue ink, appearing to read "S. Arbes".

Sarah Arbes
Acting Assistant Secretary for Legislation

Attachment

GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED -- GENERIC DRUG APPLICATIONS: FDA SHOULD TAKE ADDITIONAL STEPS TO ADDRESS FACTORS THAT MAY AFFECT APPROVAL RATES IN THE FIRST REVIEW CYCLE (GAO-19-565)

The U.S. Department of Health & Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report. FDA is committed to facilitating access to lower-cost high-quality generic medicines for the American public and has implemented targeted program enhancements aimed at reducing the number of review cycles necessary for abbreviated new drug application (ANDA) approval and increasing the overall rate of ANDA approvals. These enhancements are described in the GDUFA II (Generic Drug User Fee Amendments) commitment letter and include the following: issuance of Information Requests (IRs) and Discipline Review Letters (DRLs); meetings with applicants of complex products, including product development meetings, pre-submission meetings, and mid-cycle meetings for complex products; and funding of regulatory science research to support development and publication of new and revised product specific guidances. FDA concurs with the recommendations in the draft report and addresses each one more specifically below.

Recommendation 1

The Commissioner of FDA should take additional steps to address inconsistency in its written comments to generic drug applicants—including the clarity of writing and the content of comments—among reviewers, such as requiring additional training for reviewers.

HHS Response

FDA concurs with this recommendation and will evaluate methods to improve the clarity and content of primary reviewer comments by developing and providing training and work aids on written communication to ensure that FDA conveys deficiency comments in a clear and consistent manner to applicants. Best practices on ensuring consistency in deficiency comments would be shared with primary reviewers. In addition, we will review current training and provide coaching for secondary reviewers to exchange, compare, discuss, and improve the content and consistency of common deficiencies communicated in primary reviewer comments.

Recommendation 2

The Commissioner of FDA should assess the extent to which the timing of brand-name drug companies' drug labeling changes affect the approval of generic drug applications in the first review cycle, and take steps, as appropriate, to limit the effect of brand-name drug labeling changes on pending generic drug applications.

HHS Response

FDA concurs with this recommendation. We will identify and assess examples of applications in which the brand name drug company submitted a supplemental application for a labeling change that impacted the timeline of the generic drug approval. After gathering data, FDA will assess what particular actions could address this issue, including whether FDA has the authority to take any such identified 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, Gerardine Brennan (Assistant Director), Rebecca Rust Williamson (Analyst-in-Charge), Caroline Hale, and Elizabeth Leibinger made key contributions to this report. Also contributing were Kaitlin Farquharson, Cathy Hamann, Dan Lee, Laurie Pachter, and Vikki Porter.

Appendix IV: Accessible Data

Data Tables

Accessible Data for Number and Percentage of Generic Drug Applications Approved in the First Review Cycle, Fiscal Years 2015–2017

n/a	Number (percentage)
Total number of applications received	2,030 (100%)
Approved	240 (12%)
Not approved	1,790 (88%)

Accessible Data for Figure 1: Number and Percentage of Generic Drug Applications Approved in the First Review Cycle, Fiscal Years 2015–2017

n/a	Number (percentage)
Total number of applications received	2,030 (100%)
Approved	240 (12%)
Not approved	1,790 (88%)

Agency Comment Letter

Accessible Text for Appendix II Comments from the Department of Health and Human Services

Page 1

JUL 17 2019

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 Applications: FDA Should Take Additional Steps to Address Factors that May Affect Approval Rates in the First Review Cycle" (GAO-19-565).

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

Sincerely,

Sarah Arbes

Acting Assistant Secretary for Legislation

Attachment

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GENERAL COMMENTS FROM THE DEPARTMENT OF HEALTH & HUMAN SERVICES ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED - - GENERIC DRUG APPLICATIONS: FDA SHOULD TAKE ADDITIONAL STEPS TO ADDRESS FACTORS THAT MAY AFFECT APPROVAL RATES IN THE FIRST REVIEW CYCLE (GAO-19-565)

The U.S. Department of Health & Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report. FDA is committed to facilitating access to lower-cost high-quality generic medicines for the American public and has implemented targeted program enhancements aimed at reducing the number of review cycles necessary for abbreviated new drug application (ANDA) approval and increasing the overall rate of ANDA approvals. These enhancements are described in the GDUFA II (Generic Drug User Fee Amendments) commitment letter and include the following: issuance of Information Requests (IRs) and Discipline Review Letters (DRLs); meetings with applicants of complex products, including product development meetings, pre-submission meetings, and mid-cycle meetings for complex products; and funding of regulatory science research to support development and publication of new and revised

product specific guidances. FDA concurs with the recommendations in the draft report and addresses each one more specifically below.

Recommendation 1

The Commissioner of FDA should take additional steps to address inconsistency in its written comments to generic drug applicants-including the clarity of writing and the content of comments- among reviewers , such as requiring additional training for reviewers.

HHS Response

FDA concurs with this recommendation and will evaluate methods to improve the clarity and content of primary reviewer comments by developing and providing training and work aids on written communication to ensure that FDA conveys deficiency comments in a clear and consistent manner to applicants. Best practices on ensuring consistency in deficiency comments would be shared with primary reviewers. In addition, we will review current training and provide coaching for secondary reviewers to exchange, compare, discuss , and improve the content and consistency of common deficiencies communicated in primary reviewer comments.

Recommendation 2

The Commissioner of FDA should assess the extent to which the timing of brand-name drug companies' drug labeling changes affect the approval of generic drug applications in the first review cycle, and take steps, as appropriate, to limit the effect of brand-name drug labeling changes on pending generic drug applications.

HHS Response

FDA concurs with this recommendation. We will identify and assess examples of applications in which the brand name drug company submitted a supplemental application for a labeling change that impacted the timeline of the generic drug approval. After gathering data, FDA will assess what particular actions could address this issue, including whether FDA has the authority to take any such identified actions.

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